

STAR Ankle PMA

Panel Meeting

April 24, 2007

Company Overview

Andrew P. Greenberg

President, Link Orthopaedics, Rockaway, New Jersey

Team Members

Presenting Members

- **Andrew P. Greenberg**
President, Link Orthopaedics
- **Roger A. Mann, MD**
Oakland, CA
- **Charles Saltzman, MD**
Salt Lake City, UT
- **Michael J. Coughlin, MD**
Boise, ID

Advisory Members

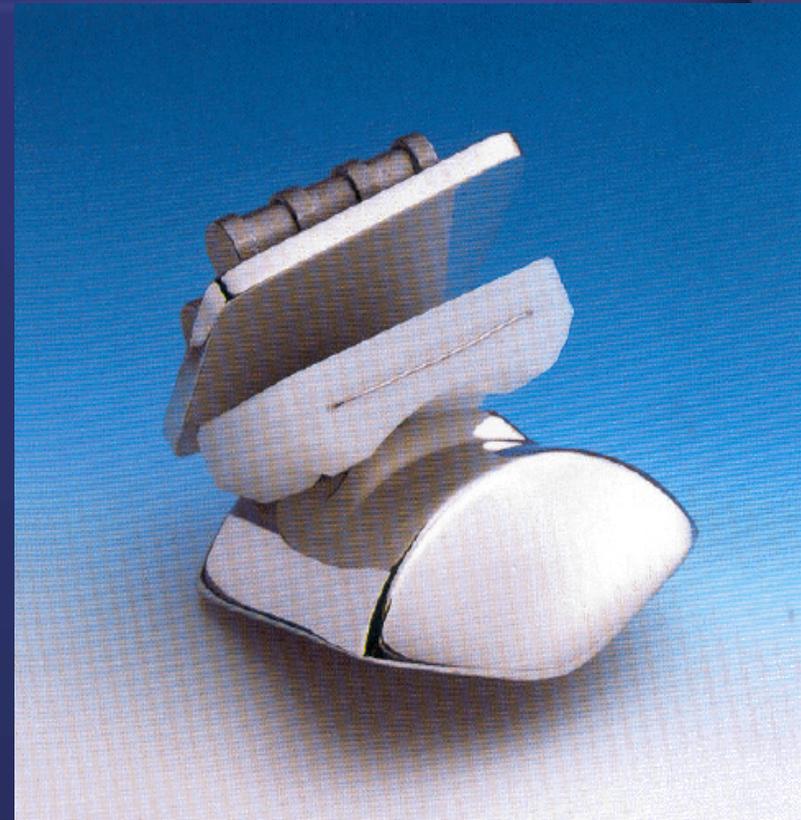
- **Thomas Clanton, MD**
Houston, TX
- **Jeanette Ahrens, PhD**
President, Pivotal Research Solutions (CRO)
- **Paul Postak, BS**
Manager, Orthopaedic Research Laboratories

Company Introduction

- **Link Orthopaedics is sister company of Waldemar Link GmbH & Co. KG, Hamburg**
- **Manufacturing total joints since 1960s**
- **International designer and manufacturer dedicated to care of orthopaedic patients**
 - **Hip**
 - **Knee**
 - **Best survivorship in Swedish Registries for hip and knee replacements**
- **All devices designed, engineered, tested, and manufactured using same materials, processes, and sterilization techniques**

STAR Ankle

- 3-part ankle
- Most widely used ankle OUS
- Marketed OUS since 1990
- CE Marked



Ankle Arthroplasty Worldwide

- **2-part ankle rarely used OUS**
- **3-part ankles used nearly exclusively OUS**
> 15 years
- **2-part cemented ankles in US**
 - 510(k) cleared
 - Used non-cemented
- **3-part ankles require data and resource intensive PMA**
 - Link pursuing PMA approval of STAR Ankle

Historical Perspective

Roger A. Mann, MD

Past-President, American Orthopedic Foot and Ankle Society

**Associate Clinical Professor of Orthopaedic Surgery
University of California School of Medicine, San Francisco, CA**

**Director Foot Fellowship Program in Adult Foot and Ankle Surgery
Oakland, CA**

Summary of Arthrodesis History

- **Prior to 1882, treatment was bracing or amputation**
- **Originated in Germany and became the standard treatment for arthritis**
- **Charnley in 1960s developed joint replacement which became standard of care for the hip, progressed to the knee**

Summary of Arthroplasty History

- Introduced in 1970s
- Early complications eliminated it as a standard procedure internationally
 - Large *two-part* implants with major bone resection
 - Cemented, constrained
- Historically difficult to revise due to amount of bone resection
- Successes in other joint replacements have led to pursuit of a refined total ankle arthroplasty

Limitations of Two-Part Ankle Designs Used in US

- **High interface stresses**
 - Bone-implant interfaces
 - Incongruent metal-polyethylene articulation
 - Doesn't dissipate transverse rotation
- **Difficulty balancing ligaments**
- **Labeled for cement fixation but commonly used cementless**
- **Specific to most commonly used**
 - Need for large bone resection
 - Requires external fixator for insertion

Three-Part Ankle Designs Used Internationally for Past 10+ Years



Ramses (FH Ortho)	STAR (Waldemar Link)	Hintegra (NewDeal)
		
Salto (Tornier)	BP (Endotec)	Alpha O.S.G. (Corin)
		

Use of European Three-Part Ankle Designs as Two-Part Ankle in US



European – 1990s



US - 2006

- Non-Cemented 3-part OUS
- Cemented 2-part for US market
 - But used non-cemented in US

Device Description

Scandinavian Total Ankle Replacement (STAR) System

- **Minimal bone resection (10-12 mm)**
- **Unconstrained**
- **Non-cemented**
 - **Porous ingrowth interface**

Three Functional Components

- **Standard cobalt chromium alloy tibial component**
- **UHMWPE mobile bearing**
- **Standard cobalt chromium alloy talar component**

Mobile Bearing Design

- **Multiple planes of motion permitted**
 - Dorsiflexion - plantarflexion
 - Transverse plane
- **Reduces shear and torque forces which can lead to loosening at the bone-metal interface**
- **Implant congruency designed to decrease polyethylene wear**
- **Near normal ankle motion**

Device Description

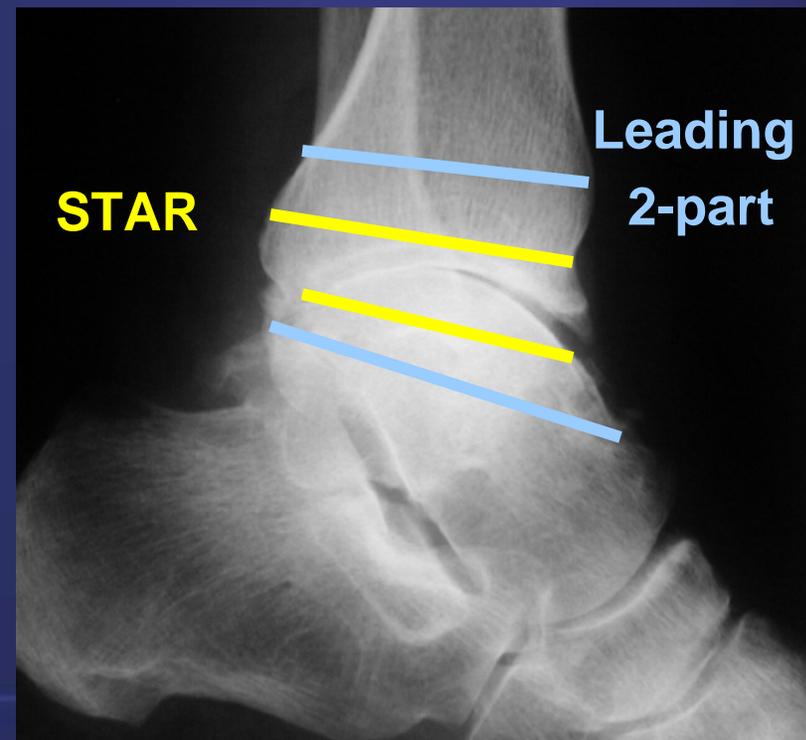


STAR Ankle Motion



STAR Ankle Bone Preservation

- **10 to 12 mm of bone resection leaves sufficient bone stock to revise the ankle arthroplasty or perform an arthrodesis**



Indications for Use

- **To replace a painful arthritic ankle due to**
 - Post-traumatic arthritis
 - Rheumatoid arthritis
 - Primary arthritis
- **Designed as an alternative to ankle arthrodesis, allowing patient to regain or retain ankle mobility and function**

Pre-Clinical Testing

Charles L. Saltzman, MD

**Professor and Chair, Department of Orthopaedics
University of Utah, Salt Lake City, UT**

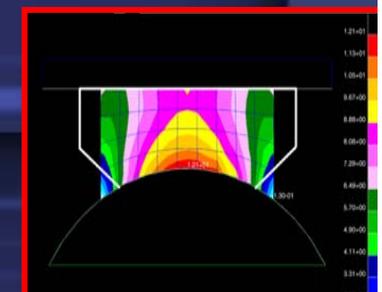
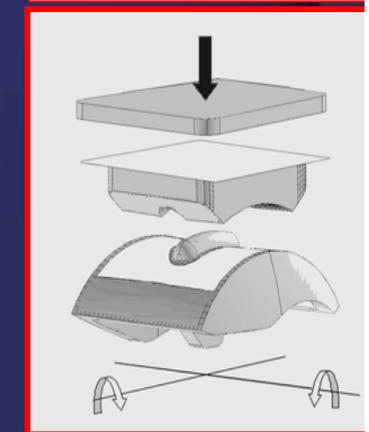
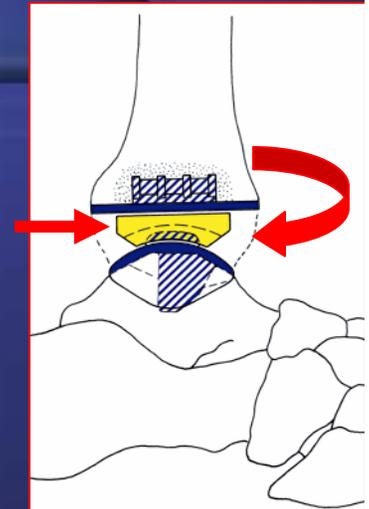
Secretary, American Orthopedic Foot and Ankle Society

In Vitro Testing of the STAR Ankle

- 1. Mechanical testing to evaluate device intrinsic stability**
- 2. Mechanical testing of contact stresses**
- 3. Finite element analysis (FEA) of stresses on surface and within polyethylene mobile bearing**
- 4. Wear testing under simulated functional use conditions**
- 5. Explant analysis**

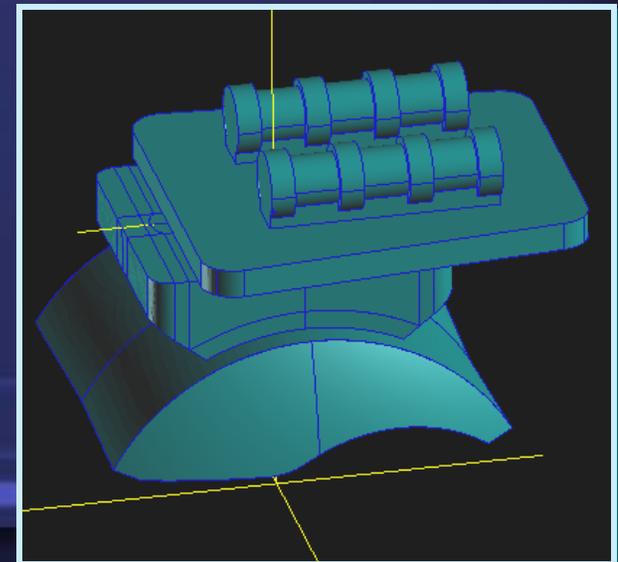
Results – Mechanical Testing

- **STAR Ankle exhibits minimal constraint in rotational, AP, and medial-lateral displacement modes**
 - Load shares with adjacent soft tissues
 - Reduces stresses at bone-implant interface
- **Contact stress testing (Fuji film) validated FEA model**
- **FEA predicted**
 - Contact stresses within tolerable limits
 - Internal stresses within tolerable limits
 - Thinner poly had higher stresses
 - Unsupported poly “overhang” had higher stresses



Wear Testing Development

- **Background on study design**
 - FDA approved IDE without requiring wear testing
 - Initiated by Link
 - Never requested by FDA
 - Testing protocol developed by Orthopaedic Research Laboratories affiliated with Cleveland Clinic (Seth Greenwald, D Phil (Oxon), Director)
- **Testing Conditions**
 - Smallest implant
 - Thinnest polyethylene
 - “Overhang”
 - Simulated continuous walking
 - Continuous high loads



Wear Testing Objectives

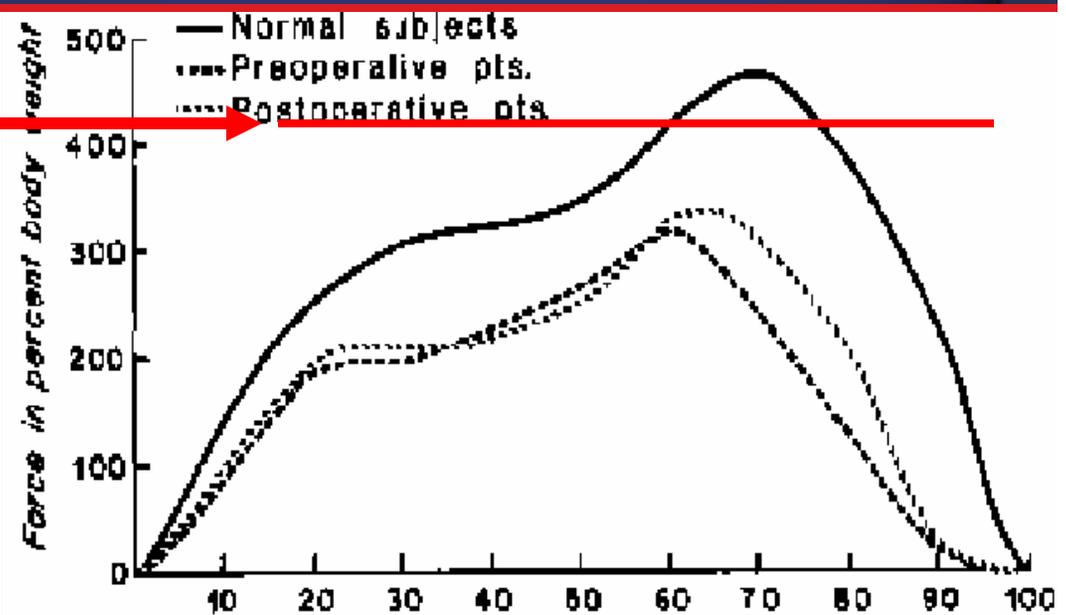
- **To simulate gradual loss of materials from a high number of normal gait motions**
- **Expected device failure modes**
 - **Wear through**
 - **Cold flow**

Pre-Clinical Testing



Wear Testing – Selection of Loading Parameters

- Continuous loading for 10 million cycles (10 yrs use)
- 3000N (@4 times BW)
- Overhang, smallest implants to replicate “worse case scenario”



Chao, Stauffer, Brewster,
Clin Orthop, 1977

Wear Testing - Results

- **No samples demonstrated functional failure, including wear through or cold flow**
- **Not designed to test ligament imbalance, deformity or transient high forces due to a traumatic event**

Explant Analysis - Description

- **Not requested by FDA during IDE process**
- **Investigational plan did not contain a formal explant protocol**
- **Explanted, shipped and stored in an uncontrolled manner**
- **Performed at FDA request after PMA submission**

Explant Analysis - Description

- **35 mobile bearings available for analysis**
 - **Pivotal, Bilateral, and Continued Access**
- **Assessments included grading of:**
 - **Burnishing**
 - **Abrasion**
 - **Pitting**
 - **Surface Deformation**
 - **Delamination**
 - **Scratching**
 - **Debris capture**
 - **Fracture**

Explant Analysis - Results

- **Most common findings**
 - Burnishing
 - Scratching
 - Pitting
 - Abrasion
- **Four mobile bearings were fractured**
 - 7, 9, 9, 10 mm (no fractures of 6 mm bearings)
 - Associated with joint imbalance / deformity / trauma
 - **Fractures are not associated with wear**
- **Loss of polyethylene on edge of component (9/35 or 26%)**
 - Associated with contact from heterotopic bone

Conclusions

- **Preclinical testing and explant analyses demonstrate suitability of the STAR Ankle for implantation and function as long-lasting prosthetic ankle replacement design**
- **Testing conditions were appropriate to evaluate mechanical stability of device**
- **Adequacy of preclinical testing confirmed by long-term European clinical experience**

Clinical Protocol Overview

U.S. STAR Ankle Clinical Studies

- **Pivotal Study (Safety and Efficacy)**
- **Bilateral Study (Safety)**
- **Continued Access Study (Safety and Efficacy)**

Objectives

- **Evaluate the safety and efficacy of the STAR Ankle vs ankle arthrodesis**
- **To treat patients with**
 - **Moderate or severe ankle pain**
 - **Loss of mobility**
 - **Loss of function due to arthritis**

Study Design

- **Multi-center clinical trial**
 - Concurrent, non-randomized controls
 - 10 STAR Ankle sites; 5 arthrodesis sites
 - 2:1 ratio of STAR Ankle : arthrodesis
- **Historical arthrodesis controls**
 - Obtained via meta-analysis
 - Provided further comparative safety data

Concurrent Control Group: Arthrodesis

- **Current surgical standard of care for patients with arthritic ankles**
- **Obliteration of ankle joint with placement of screws to maintain alignment until bone bridging occurs**

Historical Control Group: Meta-Analysis

- **Based on numerous articles in scholarly literature**
- **Captures clinical experience surrounding procedure**
- **Augments safety analysis for arthrodesis control group**
- **Originally suggested by FDA as sole control group**

Endpoints

- **Primary efficacy endpoint**
 - Mean total Buechel-Pappas (BP) score
- **Composite safety endpoint**
(not specified as primary in protocol)
 - No major complications
 - No device failure, revisions or removal
 - Radiographic criteria
 - STAR Ankle: No radiographic evidence for device loosening or migration
 - Control: No radiographic evidence for non-union, delayed union, or malunion

Sample Size

- **Non-inferiority study**
 - 10 point efficacy delta on mean BP scale
 - 15% safety delta
- **Sample size estimate**
 - Efficacy: 24 STAR Ankle and 12 arthrodesis
 - Safety: 134 STAR Ankle and 67 arthrodesis
 - Study powered based on safety endpoint
- **Patients enrolled**
 - 158 STAR Ankle and 66 arthrodesis

Major Inclusion Criteria

- **Primary ankle arthritis, posttraumatic arthritis or rheumatoid arthritis**
- **Moderate or severe pain**
(BP pain score \leq 20 on a 40 point scale)
- **Loss of mobility and function of the ankle**
(Total BP score $<$ 50 on a 100 point scale)
- **Failed trial of a foot and ankle orthosis and/or analgesic medication for 3 months**
- **Minimum 6 months of conservative treatment**

Major Exclusion Criteria

- **Hindfoot malpositioned >35 degrees or forefoot malalignment which would preclude a plantigrade foot**
- **Avascular necrosis of the talus or tibia**
- **Severe osteopenia or inadequate bone stock**
- **Insufficient ligament support**
- **Active or prior deep infection in the ankle joint or adjacent bones**
- **Neuromuscular impairment**

Postop Protocol

- **Arthrodesis**
 - Weeks 0-6: below knee cast - NWB
 - Weeks ≥ 7 : below knee cast - PWB \rightarrow WB
- **STAR Ankle**
 - Weeks 0-2: splint immobilized, NWB
 - Weeks 2-4: below knee cast, 50% WB
 - Weeks 4-6: below knee cast, 100% WB

Follow-up Visits

- **Baseline**
- **Operative**
- **Follow-up**
 - 2-3 weeks
 - 6 weeks
 - 3 months
 - 6 months
 - 12 months
 - 24 months

Success Endpoints

- **Efficacy Success**
 - ≥ 40 point improvement in 100 point BP score
- **Safety Success**
 - No radiographic failure,
 - No device failure, revisions or removal, and
 - No major complications
- **Overall Patient Success**
 - Efficacy success and safety success

Secondary Efficacy Endpoints

- **Pain Visual Analog Scale (VAS)**
(100mm scale)
- **Patient Satisfaction (Coughlin rating)**
- **Quality of Life (SF-36)**
- **Medication Usage**

Efficacy: Buechel-Pappas Scale (Total 100 points)

- **Pain** (40 points)

- **Function** (40 points)
 - 5 subscales (8 points each)
 - Limp, Stairs, Standing, Support, Walking

- **Examination** (20 points)
 - Range of Motion (15 points)
 - Deformity (5 points)

Choice of BP score for Efficacy Endpoint

- Multiple ankle scales considered in 1999
- None validated in ankle replacement patients
- BP scale previously used to evaluate total ankle arthroplasty with both clinical and functional measures
- BP subscale considerations
 - Bias potentially favors STAR: ROM
 - Bias potentially favors arthrodesis: Pain
 - All subscales important in evaluating patient success

Major Complications: Definition

- **Surgical intervention for:**
 - Infection
 - Wound problems
 - Fracture
 - Bony changes
 - Cysts, osteolysis
 - AVN
 - Heterotopic bone formation

Radiographic Review

- **Arthrodesis**
 - Investigator evaluated fusion status
 - No independent confirmation of fusion status
- **STAR Ankle**
 - Radiographs evaluated for all time periods using a zonal analysis developed prior to the study
 - All radiographs were evaluated by one central reviewer

Arthrodesis Fusion Status

- **Union:**
 - **>50% bony bridging**
 - **≤4 months**
- **Delayed Union:**
 - **>50% bony bridging**
 - **4 to 6 months**
- **Nonunion:**
 - **<50% bony bridging**
 - **>6 months**

STAR Ankle Radiographic Review

- **Goal** to identify radiographic signs that predict eventual failure: clinically significant loosening or migration
- Pre-study, no information available to guide development of radiographic analysis plan for uncemented ankle replacement
- Initial PMA radiographic analysis was inconsistent with goal and protocol
- Revised radiographic analysis is more accurate and consistent with original intent of protocol for an uncemented ankle

Concerns with Initial STAR Ankle PMA Radiographic Analysis

- 1. Inappropriate carrying forward of radiographic information**
 - In initial PMA analysis, STAR Ankle subjects who were not radiographic successes at 6 or 12 months were considered failures at 24 months, regardless of 24 month results
 - Seven (7) of these subjects met radiographic success by 24 months, and should be considered radiographic successes

Concerns with Initial STAR Ankle PMA Radiographic Analysis

2. **Inappropriate interpretation of early radiographic findings as predictive of long-term clinical failure**
 - **Early settling of an implant that subsequently stabilizes was not found predictive of 24 month clinical outcomes**
 - **Five (5) subjects initially classified as safety failures**
 - **Had no further change in radiographs**
 - **Had satisfactory clinical results at 48 months**
 - **Should be considered radiographic successes at 24 months**

Bilateral Study

- **Single arm multi-center study of bilateral treatment of 21 patients**
 - Patients initially enrolled in pivotal or continued access studies who developed bilateral disease, or
 - Patients presenting with bilateral disease
- **Safety analysis only**
 - Patients that transferred were only included in efficacy study data until point of contralateral ankle treatment

Continued Access Study

- **Between 2002 and 2004, Link received FDA approval for a multi-center registry continued access study**
 - **Three phases of 150 patients each**
 - **Same sites that participated in pivotal study also participated in continued access study**
 - **Co-investigators at some sites were able to perform STAR Ankle procedures**

STAR Ankle Anterior Surgical Procedure

- At study outset, anterior approach less familiar approach than lateral approach
- Used for all ankle arthroplasties
- Experience and awareness increased nationally during course of study
- Increasingly taught in both residency and fellowship programs



Anterior Approach Challenges

- **Susceptible to wound problems**
 - Thinner skin / less subcutaneous fat
 - Incision runs down center of an angiosome
- **Susceptible to transient or permanent sensory loss on medial dorsal aspect of foot**
 - Stretch or transection of a fine terminal branch from medial branch of superficial peroneal nerve

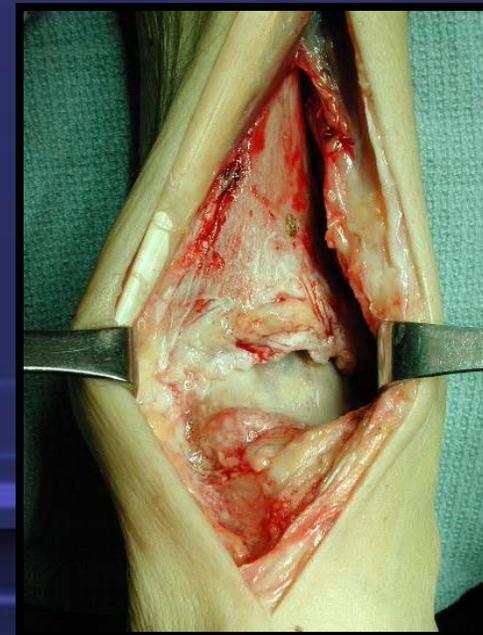


Pivotal Study Refinements

- **Surgery refinement**
 - Instrumentation
 - Technique
- **Better patient selection**
- **More rigorous post-op patient education**

Surgical Technique Modifications

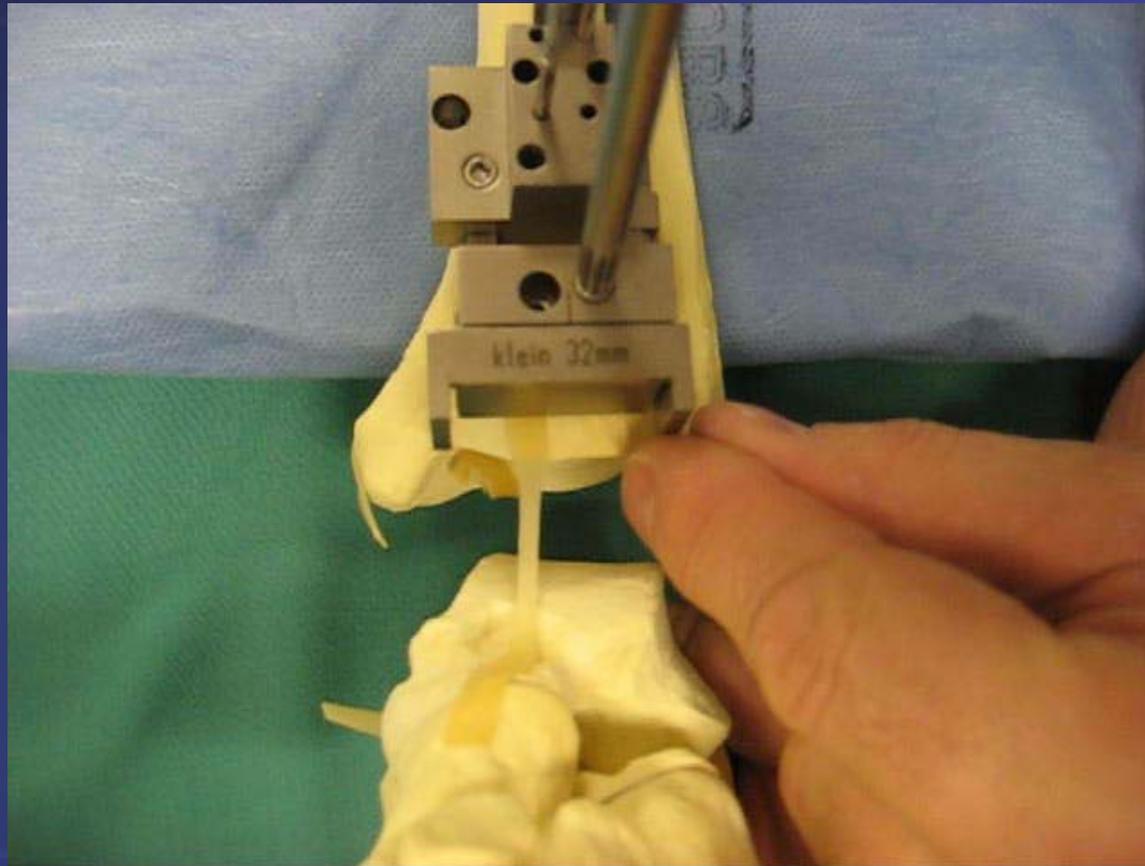
- **Wound Problems**
 - Lengthened the incision
 - Eliminated self-retaining retractors
 - Eliminated skin staples
- **Intra-operative Fractures**
 - Protected at risk medial malleolus with two K-wires
- **Implant Selection**
 - Generally inserted thicker polyethylene mobile bearings
 - Generally downsized talar components



Instrumentation Modifications

- **Better capturing of tibial saw blade decreased the bony nicks, decreasing incidence of fracture**
- **Adjustable medial/lateral block facilitating precise device placement and decreasing incidence of fracture and bone problems**

Instrumentation Modifications



Instrumentation Modifications

- **Addition of talar trials and talar fin tamp helped assess accuracy of bone preparation and improved device placement**



Instrumentation Modifications



Patient-Related Modifications

- **Patient Selection**
 - Increased awareness of difficulties with coronal plane deformity
 - Exclusion of patients with peripheral neuropathy
- **Patient Instruction**
 - Increased emphasis to ensure patient compliance with post-operative recovery regimes



Summary

- **Preclinical Testing**
- **Radiographic Review**
- **Lessons Learned**

Summary

- **Preclinical Testing**
 - Adequate
 - Improved understanding of mechanics
- Radiographic Review
- Lessons Learned

Summary

- **Preclinical Testing**
- **Radiographic Review**
 - **Revised Analysis**
 - **More Clinically Appropriate**
- **Lessons Learned**

Summary

- Preclinical Testing
- Radiographic Review
- **Lessons Learned**
 - **Improved Safety**

Study Results

Michael J. Coughlin, MD

**Clinical Professor of Orthopedic Surgery
Oregon Health Sciences University, Portland, Oregon**

Director, Idaho Foot and Ankle Fellowship, Boise, Idaho

Past-President, American Orthopedic Foot and Ankle Society

Past-President, International Federation of Foot and Ankle Societies

Clinical Centers - STAR

Centers	Principal Investigators
Dr. Roger Mann, Inc., CA	Roger Mann, MD
Univ. of Iowa, Orthopedic Surgery, IA	Charles Saltzman, MD
Foot & Ankle, Inc., ID	Michael Coughlin, MD
Univ. Texas Medical School, TX	Thomas Clanton, MD
Mayo Clinic, FL	James DeOrio, MD
Orthopaedic Foot & Ankle Center, OH	Thomas Lee, MD
Kansas Univ. Medical Center, KS	Greg Horton, MD
Florida Orthopaedic Institute, FL	Arthur Walling, MD
Baylor Research Institute, TX	James Brodsky, MD
Duke Univ. Medical Center, NC	James Nunley, MD

Clinical Centers – Control

Centers	Principal Investigators
USC School of Medicine, CA	David Thordarson, MD
Hospital for Special Surgery, NY	Jonathan Deland, MD
Stanford Univ. Medical Center, CA	Loretta Chou, MD
Extreme Orthopaedics, PA	Keith Wapner, MD
Miller Orthopaedic Clinic, NC	Robert Anderson, MD

Data Accountability

- **Enrollment**
 - **STAR Ankle: 158**
 - **Arthrodesis: 66**
- **Arthrodesis Enrollment and Follow-up**
 - **Patient and Investigator reluctance to comply with extensive follow-up and record-keeping study requirements for patients receiving only the standard of care**

Data Accountability

	12 months		24 months	
	STAR	Control	STAR	Control
Enrolled	158	66	158	66
Deaths	3	0	4	1
Device Removed and LTF	1	0	2	0
Transferred to Bilateral ARM	2	0	2	0
Actual	147	53	145	48
% Follow-up	96.7	81.5	96.7	77.4

Analysis Populations

- **Intent-to-Treat (ITT) Population**
 - All patients treated in the study
- **Completers Population**
 - Patients for whom the necessary data for a particular endpoint was present at the time of database closure
 - Numbers can be different for each endpoint at a follow-up visit
- **Per Protocol (PP) Population**
 - Completers with no major protocol deviations, in window visits, and who were not considered bilateral

Patient Population Identification for Success Rates

	Safety		Efficacy		Patients	
	STAR	Control	STAR	Control	STAR	Control
Theoretical (ITT)	158	66	158	66	158	66
Missing Data	16	14	16	19	16	15
Completers	142	52	142	47	142	51
Eligibility Violations	3	1	3	1	3	1
Protocol Deviations	3	8	1	7	1	7
Bilateral Patients	10	3	11	3	10	3
Per Protocol	126	40	127	36	128	40

Baseline Characteristics

	STAR (N=158)	Control (N=66)	p-value
Gender			
Male	78 (49.4%)	30 (45.5%)	0.593
Female	80 (50.6%)	36 (54.5%)	
Race			
Caucasian	152 (96.2%)	60 (90.9%)	0.205
Hispanic	1 (0.6%)	3 (4.5%)	
African American	4 (2.5%)	2 (3%)	
Other	1 (0.6%)	1 (1.5%)	

Baseline Characteristics

	STAR (N=158)	Control (N=66)	p-value
Age	62.7 (12.6)	57.1 (12.3)	0.004
Height	67.3 (3.7)	67.0 (4.5)	0.612
Weight	180.9 (34.9)	185.6 (38.6)	0.378
BMI	28 (4.8)	29.1 (5.8)	0.409

Age was evaluated as a covariate of patient success

Baseline Diagnosis

	STAR (N=158)	Control (N=66)	p-value
Primary Arthritis	62 (39.2%)	19 (28.8%)	0.054
Post-traumatic Arthritis	76 (48.1%)	43 (65.2%)	
Rheumatoid Arthritis	20 (12.7%)	4 (6.1%)	

Patients with RA are expected to have lower BP scores because multiple joint involvement change in pain reduction and return to function, a higher complication rate due to intrinsic bony and soft tissue issues

Baseline BP Scores

	STAR (N=158)	Control (N=66)	p-value
Deformity	2.8 (1.3)	2.9 (1)	0.441
Function	18.6 (5.7)	21.1 (6.1)	0.005
Pain	10.6 (3.9)	12 (5)	0.056
ROM	8.7 (3.6)	7 (4)	0.002
Total	40.8 (7.4)	43 (8.8)	0.058

STAR Ankle patients baseline BP scores slightly worse than control patients

Comparability of Groups at Baseline

- **Generally comparable**
 - **Gender**
 - **Weight**
 - **Height**
- **STAR Ankle more debilitated at baseline**
 - **Rheumatoid arthritis**
 - **Older**
 - **Lower BP scale**
 - **More pain**
 - **Lower function**

Operative Characteristics

	STAR (N=158)	Control (N=66)	p-value
Operative Time (hours)	2.2 (0.5)	2.4 (1.2)	0.613
Anesthesia Time (hours)	3.1 (0.7)	3.2 (1.3)	0.784
Estimated Blood Loss (cc)	53.1 (44.5)	75.3 (89.9)	0.318
Length of Stay (days)	3.1 (1.9)	3 (1.3)	0.810

Primary Efficacy Endpoint: Mean BP Score

	12 Months			24 Months		
	STAR (n=143)	Control (n=53)	p-value	STAR (n=142)	Control (n=47)	p-value
Total *	80.7 (14.3)	65.9 (17.0)	<0.001	81.6 (14.0)	69.7 (16.8)	<0.001
Total ** (No ROM)	68.3 (13.8)	63.6 (16.9)	0.048	69.2 (13.4)	66.4 (16.5)	0.25

** Primary endpoint based on Total BP score - showed superior efficacy where study hypothesis only required demonstration of non-inferiority*

*** BP without ROM – post hoc analysis requested by FDA; does not reflect intended benefit of any ankle arthroplasty; non-inferiority still demonstrated*

Improvement in BP Scores

	12 Months			24 Months		
	STAR (n=144)	Control (n=53)	p-value	STAR (n=143)	Control (n=48)	p-value
Deformity	1.8 (1.3)	0.5 (1.2)	<0.001	1.9 (1.3)	0.4 (1.2)	<0.001
Function	13.6 (7.9)	9.5 (8.1)	0.002	13.4 (7.3)	9.7 (8.7)	0.004
Pain	20.6 (9)	18.3 (9.6)	0.126	21.5 (9.6)	19.2 (9.4)	0.14
ROM	3.7 (3.7)	-4.9 (5.2)	<0.001	3.6 (3.7)	-3.7 (5.1)	<0.001
Total	39.7 (15)	23.3 (15.9)	<0.001	40.5 (15.1)	26.3 (17.1)	<0.001

Significantly greater improvement in deformity subscore in STAR group

Improvement in BP Scores

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Significantly greater improvement in function subscore in STAR group

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Total	39.7 (15)	23.3 (15.9)	<0.001	40.5 (15.1)	26.3 (17.1)	<0.001

Comparable improvement in pain relief between groups

Improvement in BP Scores

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	STAR (n=144)	Control (n=53)	p-value	STAR (n=143)	Control (n=48)	p-value
Deformity	1.8 (1.3)	0.5 (1.2)	<0.001	1.9 (1.3)	0.4 (1.2)	<0.001
Function	13.6 (7.9)	9.5 (8.1)	0.002	13.4 (7.3)	9.7 (8.7)	0.004
Pain	20.6 (9)	18.3 (9.6)	0.126	21.5 (9.6)	19.2 (9.4)	0.14
ROM	3.7 (3.7)	-4.9 (5.2)	<0.001	3.6 (3.7)	-3.7 (5.1)	<0.001
Total	39.7 (15)	23.3 (15.9)	<0.001	40.5 (15.1)	26.3 (17.1)	<0.001

Significantly greater improvement in ROM subscore in STAR group

Improvement in BP Scores

	12 Months			24 Months		
	STAR (n=144)	Control (n=53)	p-value	STAR (n=143)	Control (n=48)	p-value
Deformity	1.8 (1.3)	0.5 (1.2)	<0.001	1.9 (1.3)	0.4 (1.2)	<0.001
Function	13.6 (7.9)	9.5 (8.1)	0.002	13.4 (7.3)	9.7 (8.7)	0.004
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ROM	3.7 (3.7)	-4.9 (5.2)	<0.001	3.6 (3.7)	-3.7 (5.1)	<0.001
Total	39.7 (15)	23.3 (15.9)	<0.001	40.5 (15.1)	26.3 (17.1)	<0.001

Improvement in total BP score was significantly higher in STAR group

Improvement in BP Scores

	12 Months			24 Months		
	STAR (n=144)	Control (n=53)	p-value	STAR (n=143)	Control (n=48)	p-value
Deformity	1.8 (1.3)	0.5 (1.2)	<0.001	1.9 (1.3)	0.4 (1.2)	<0.001
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ROM	3.7 (3.7)	-4.9 (5.2)	<0.001	3.6 (3.7)	-3.7 (5.1)	<0.001
Total	39.7 (15)	23.3 (15.9)	<0.001	40.5 (15.1)	26.3 (17.1)	<0.001
Total (ROM Removed)	35.9 (14.3)	28.3 (15.6)	0.001	36.9 (14.5)	30 (15.8)	0.006

Despite design of ankle arthroplasty to retain range of motion, significant improvement still shown without range of motion

Improvement in BP Function Scores

	12 Months			24 Months		
	STAR	Control	p-value	STAR	Control	p-value
Stairs (8 pts)	1.6 (2.1)	1.2 (2.1)	0.243	1.6 (2.1)	0.9 (2)	0.039
Standing (8 pts)	3.5 (2.4)	2.0 (2.8)	<0.001	3.4 (2.8)	1.7 (3.3)	<0.001
Support (8 pts)	1.6 (2.5)	0.7 (2.2)	0.02	1.7 (2.2)	0.8 (1.9)	0.016
Walking (8 pts)	2.6 (2)	2.2 (2.1)	0.165	2.6 (1.9)	2.7 (1.9)	0.746
Limp (8 pts)	4.2 (2.3)	3.2 (2.5)	0.007	4.1 (2.2)	3.4 (3.4)	0.114
Total (40 pts)	13.6 (7.9)	9.5 (8.1)	0.002	13.4 (7.3)	9.7 (8.7)	0.004

•Statistically significant improvement in overall function and 3 function sub-scores (stairs, standing, and support) at 24 months

•Walking is based upon flat ground and not on an incline, therefore no difference would be expected between the groups

Efficacy Success

BP Score	STAR			Control			p-value
	n	N	%	n	N	%	
≥ 40 point Improvement							
12 Month	84	143	58.7%	7	53	13.2%	<0.001
24 Month	83	142	58.5%	7	47	14.9%	<0.001
≥ 25 point Improvement (ROM Removed)							
12 Month	113	143	79.0%	34	53	64.2%	0.033
24 Month	114	142	80.3%	34	47	72.3%	0.25

Significantly more patients in STAR group with ≥40 point improvement in total BP score

Safety Success Rates: Initial PMA Analysis

	12 months				24 months			
	STAR		Control		STAR		Control	
	n/N	%	n/N	%	n/N	%	n/N	%
Safety Success	109/136	80.1	50/57	87.7	101/142	71.1	43/52	82.7
No Revisions or Removals	125/136	91.9	54/57	94.7	122/142	81.0	47/52	90.4
No Major Complications	126/136	92.6	56/57	98.2	128/142	90.1	51/52	98.1
Radiographic Success	120/131	91.6	51/57	89.5	117/138	84.8	46/52	88.5

Inappropriate Initial PMA Radiographic Analysis

- **Inappropriate carrying forward of radiographic information**
 - Seven (7) of these subjects met radiographic success by 24 months, and should be considered radiographic successes
- **Inappropriate interpretation of early radiographic findings as predictive of long-term clinical failure**
 - Five (5) subjects initially classified as safety failures
 - Had no further change in radiographs
 - Had satisfactory clinical results at 48 months
 - Should be considered radiographic successes at 24 months

Impact of Appropriate Radiographic Analysis

- **Additional 12 subjects considered *radiographic* successes at 24 months**
- **Thus, 12 additional *safety* successes at 24 months as subjects met all other safety success criteria**

Components of Safety Endpoint at 24 Months: Revised Analysis

Components of Safety Endpoint	STAR		Control	
	n/N	%	n/N	%
No Revisions or Removals	122/142	85.9%	47/52	90.4%
No Major Complications	128/142	90.1%	51/52	98.1%
Radiographic Success				
a) Initial PMA Analysis	117/138	84.8%	46/52	88.5%
b) No Carrying Forward of Early Radiographic Findings	124/137	90.5%	NA	NA
c) Radiographic Findings Not Predictive of Clinical Failure	129/137	94.2%	NA	NA

Safety Success Rates at 24 Months: Revised Analysis

	STAR		Control		Lower Bound of 90% CI	Delta Met?
	n/N	%	n/N	%		
Safety Success at 24 Months						
a) Initial PMA Analysis	101/142	71.1%	43/52	82.7%	-22.2%	No
b) No Carrying Forward of Early Radiographic Findings	108/142	76.1%	NA	NA	-17.1%	No
c) Radiographic Findings Not Predictive of Clinical Failure	113/142	79.6%	NA	NA	-13.4%	Yes

–Non-inferiority of STAR based on clinically appropriate radiographic analysis

–Safety success in control group would be lower if adjusted for under reporting of delayed union rate

Impact of Radiographic Analysis

- Safety endpoint met in pivotal study with appropriate STAR radiographic analysis
- Control success overestimated
 - Under reporting of fusion failure rates by using investigator classifications
 - Expected 86.5% fusion rate because 13.5% patients are not full weight-bearing at 4 month visit
- The more appropriate the analysis (in both STAR and Control groups), the more comparable the safety success rates
- Safety success rate in STAR Ankle Continued Access group non-inferior to control group (to be further discussed)

Patient Success Rates at 24 Months

Overall Patient Success	STAR		Control	
	n/N	%	n/N	%
a) Initial PMA Analysis	64/142	45.1%	7/51	13.7%
b) No Carrying Forward of Early Radiographic Findings	68/142	47.9%	NA	NA
c) Radiographic Findings Not Predictive of Clinical Failure	70/142	49.3%	NA	NA

Significantly higher patient success rates ($p < 0.0001$) for all comparisons

Patient Success Rates at 24 Months: ROM Removed

Overall Patient Success – ROM removed	STAR		Control	
	n/N	%	n/N	%
a) Initial PMA Analysis	87/141	61.7%	33/51	64.7%
b) No Carrying Forward of Early Radiographic Findings	93/141	66.0%	NA	NA
c) Radiographic Findings Not Predictive of Clinical Failure	96/141	68.1%	NA	NA

Comparable patient success rates even with ROM removed

Efficacy Measures – Pain VAS

Improvement from Baseline	12 Months			24 Months		
	STAR (n=144)	Control (n=51)	p-value	STAR (n=144)	Control (n=45)	p-value
Mean (S.D.)	51.1 (24.3)	43.5 (27.0)	0.118	51.8 (26.5)	44.6 (27.3)	0.089

	<u>STAR</u>	<u>Control</u>
Preop	71.1 (17)	65.8 (19)
24 months	19.5 (20)	17.9 (20)

Efficacy Measures – Patient Satisfaction

	12 Months			24 Months		
	STAR	Control	p-value	STAR	Control	p-value
Excellent	69 (49%)	20 (38%)	0.108	67 (47%)	22 (47%)	0.968
Good	50 (35%)	20 (38%)		56 (39%)	18 (38%)	
Fair	21 (15%)	10 (19%)		16 (11%)	5 (11%)	
Poor	1 (1%)	3 (5%)		4 (3%)	2 (4%)	

Adverse Events Prior to Discharge

	STAR (N=158)	Control (N=66)
Bone Fracture *†	15 (9.5%)	1 (1.5%)
Pain	12 (7.6%)	3 (4.5%)
Nerve Injury * (Superficial Branch of Peroneal Nerve)	9 (5.7%)	
Soft Tissue Edema	3 (1.9%)	
Decreased ROM ‡	3 (1.9%)	
Wound Problem *	2 (1.3%)	

* ***Events due to incision or STAR procedure that would not be expected to occur in the control population***

† ***Not reported as AE in control group because required for arthrodesis***

‡ ***Event not reported in arthrodesis population because expected***

Operative Difficulties

- **Intraoperative fractures in STAR Ankle group**
 - **Resulted in change in surgical technique**
 - **Nearly half occurred at one site but none at this site after change in surgical technique**
- **Intraoperative fractures in arthrodesis group**
 - **Routine part of procedure (100%)**

Adverse Events

Operative Site Events	STAR (N=158)	Control (N=66)
Pain	69 (43.7%)	32 (48.5%)
Nerve Injury	32 (20.3%)	5 (7.6%)
Bone Fracture	28 (17.7%)	2 (3.0%)
Soft Tissue Edema	25 (15.8%)	4 (6.1%)
Decreased ROM	10 (6.3%)	Expected
Wound Problem	32 (20.3%)	4 (6.1%)
Infection	7 (4.4%)	5 (7.6%)
Bony Changes	12 (7.6%)	NA
Delayed / Non-Union	NA	6 (11.5%) – 7 (13.5%)

Adverse events up to 24 months of follow-up

Superficial Peroneal Nerve



Adverse Events - Perspective

Op Site Events	
Pain	Comparable in both groups
Nerve Injury	Superficial branch of peroneal nerve (clinically insignificant); comparable to TKA
Bone Fracture	Rarely significant; intrinsic to arthrodesis; reduced in Continued Access
Soft Tissue Edema	Characteristic of all arthroplasties; transient; readily apparent with early cast changes; seen with early weight-bearing
Decreased ROM	Intrinsic to arthrodesis
Wound Problem	Characteristic of anterior approach; improved in Continued Access with technique changes
Infection	Lower in STAR group
Bony Changes	Similar to non/delayed-union rate

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STAR Adverse Events by Major Complications

Operative Site Adverse Events	Patients	Major Complication
Bone Fractures		
Intra-operative	15	0
Post-operative	14	4
Bony Changes	12	4
Infection	7	1
Wound Problem	32	6
Nerve Injury	32	0

Adverse events up to 24 months of follow-up

Most STAR operative site adverse events did not result in major complications

Surgical Interventions

	STAR	Control
# Surgical Interventions	33	9
# Patients with Surgical Interventions	26 (16.5%)	7 (10.6%)
Intervention Type		
Revision	11 (7.0%)	3 (4.5%)
Removal	2 (1.3%)	4 (6.1%)
Reoperation	8 (5.1%)	0 (0%)
Other Intervention	10 (6.3%)	1 (1.5%)

Surgical interventions up to 24 months follow-up

STAR Surgical Interventions (Revisions and Removals)

	Up to 24 months
Components Revised or Removed	# Patients
All Three Components	2
Mobile Bearing Component Only	5
Mobile Bearing and Talar Components	1
Mobile Bearing and Tibial Components	2
Other (originally misclassified)	(2)
Total	12 (10)

Surgical Interventions in Perspective

- **Only 5 of 12 interventions involved major surgery (3.2%, 5/158)**
 - No conversions to arthroplasty
 - 2 conversions to arthrodesis
 - 3 mobile bearing/metal revisions
- **Control results in study much better than reported in arthrodesis literature**
 - Pivotal STAR intervention rate comparable to that in historical arthrodesis controls
 - Continued Access intervention rate substantially lower (to be further discussed)

Major Complications

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

Major complications up to 24 months follow-up

*Bone problems = osteolysis, bone fracture, exostosis

** **Delayed union and malunion not included**

Major Complications in Perspective

- **Definition of major complications focused largely on arthroplasty**
 - **Wound problems associated with anterior approach used for all ankle arthroplasty procedures**
 - **Bone problems a natural consequence of a motion-preserving device**
 - **Not expected with fusion**
 - **Seen with other weight-bearing arthroplasty devices (e.g., hip and knee)**

Addressing Major Complications

- **Changes in surgical technique for the Continued Access study reduced major complications**
 - **Wound problems**
 - Extended incision
 - Hand retraction
 - Two-layer suture closure
 - **Bone problems**
 - K-wire to minimize intra-operative fractures
 - Downsize talar components
 - Use of new saw guides, trials, and tamps

Meta-Analysis Context

- **Anticipated difficulty enrolling patients to arthrodesis control**
 - Permanent loss of ankle mobility
 - Degeneration of adjacent joints
 - Availability of FDA-cleared ankle prosthesis
 - Reluctance of patients to comply with extensive long-term protocol requirements
- **Meta-analysis of published arthrodesis literature to supplement pivotal study safety data**

Meta-Analysis

- **12 published articles, 1983-1999**
- **413 total arthrodesis cases (range: 11-101)**
- **Mean follow-up/study: 2-10 years**
- **Patient population similar to Pivotal Study**
- **Operative technique similar to arthrodesis control group**
- **Literature complication rates similar to IDE pivotal study arthrodesis controls**

Meta-Analysis Results

	Historical Control	Pivotal Study	
		STAR	Control
Number of Cases (N)	413	158	66
Surgical Interventions due to Major Complications	9 (2.2%)	16 (10.1%)	1 (1.5%)
Radiographic evidence of nonunion, delayed union, malunion	48 (11.6%)		6 (9.1%)
Device failure, revision or removal	49 (11.9%)	20 (12.7%)	5 (7.6%)
Failures	--	41 (28.9%)	9 (18.4%)

Meta-Analysis Overview

- **Control results were much better than historical results for ankle arthroplasty**
- **Safety results observed in the STAR group of the Pivotal Study are representative of historical controls**
- **Safety profile of STAR based upon period when the technique was being refined**

Continued Access Study

Independent X-ray Review Accountability



- In December 2005, FDA raised a question regarding radiographic review for Continued Access patients
- Company performed radiographic review on patients in first arm of Continued Access study who had 24 month follow-up visit in PMA database (n=120)
- All 24 month radiographs then available (85 of 120 patients) were reviewed
- 5 of 85 patients had incomplete radiographic data, due to quality of x-rays or position of ankle, to determine status of success/failure
- Independent radiographic review performed by Medical Metrics, Inc. (Houston, TX)
 - Fewer failures identified in this review than pivotal study

Success Rates at 24 Months – Based on Patients with Radiographic Reviews

	Control		Pivotal STAR **		Continued Access*		Delta Met? (CA vs. Control)
	n/N	%	n/N	%	n/N	%	
Overall Patient Success	7/51	13.7%	70/142	49.3%	61/81	75.3%	Delta N/A (p<0.0001)
Efficacy Success	7/47	14.9%	83/142	58.5%	70/83	84.3%	Yes
Safety Success	47/52	90.4%	113/142	79.6%	72/81	88.9%	Yes

* Based on subset of patients with independent radiographic review; initial radiographic analysis

** Based on clinically appropriate radiographic analysis

— All Continued Access success rates higher than in Pivotal Study

Safety Success Rates at 24 Months – Imputed Radiographic Results for Continued Access Patients

Safety Success Rate	Control		Pivotal STAR		Continued Access*		Delta Met? (CA vs. Control)
	n/N	%	n/N	%	n/N	%	
a) Initial PMA Analysis	43/52	82.7%	101/142	71.1%	176/225	78.2%	Yes
b) Clinically Appropriate Analysis	43/52	82.7%	113/142	79.6%	189/225	84.0%	Yes

**For Continued Access patients without independent radiographic review, safety success rate based on imputing radiographic success rate from Pivotal Study*

Surgical Interventions at 24 Months

	Pivotal STAR	Continued Access STAR
Number of Patients	158	352
# Patients with Interventions	26 (16.5%)	26 (7.4%)
Intervention Type		
Revision, Removal	12 (7.6%)	12 (3.4%)
Other Intervention	18 (11.4%)	15 (4.3%)

- *Much lower rate of surgical interventions observed in Continued Access Study as compared to Pivotal Study*

Major Complications at 24 Months

Major Complication Classification	Pivotal STAR	Continued Access STAR
Number of Patients	158	352
Any Major Complication	14 (8.9%)	17 (4.8%)
Wound Problems	5 (3.2%)	5 (1.4%)
Infection	2 (1.3%)	3 (0.8%)
Bone Problems	8 (5.1%)	10 (2.8%)
Wound Problems and Infection	1 (0.6%)	0 (0%)

- *Much lower rate of major complications in Continued Access study compared to Pivotal Study*
- *Decrease in major complications likely related to changes in surgical technique and instrumentation*

Surgical Interventions and Major Complications in Perspective

	Pivotal		Continued Access
	Control (N=66)	STAR (N=158)	STAR (N=352)
Revision/ removal	6 (9.1%)	12 (7.6%)	12 (3.4%)
Major complication	1 (1.5%)	14 (8.9%)	17 (4.8%)
Either	7 (10.6%)	22 (13.9%)	25 (7.1%)
			All STARs (47/510) = 9.2%

- *Substantial decrease in Continued Access*
- *Revision/removal and major complications comparable to controls*
- *Comparable rates to historical arthrodesis*

Conclusions

- **STAR Ankle Overall Conclusions**
 - Superior patient success results

- **STAR Ankle Safety Conclusions**
 - Comparable safety profiles as compared with both concurrent and historical controls

Conclusions

- **STAR Ankle Efficacy Conclusions**
 - Superior efficacy results at 12 and 24 months for:
 - Mean BP score
 - ≥ 40 point improvement in BP Score
 - Efficacy results for mean BP score minus ROM subscore:
 - Superior at 12 months
 - Non-inferior at 24 months
 - Clear improvement in function

Conclusions

- **Continued Access Study Conclusions**
 - **Modifications to surgical procedures and techniques resulted in lower adverse event rates**
 - **Physician experience associated with improved safety, efficacy and overall outcomes**
 - **Superior success rates at 12 and 24 months for:**
 - Overall success
 - Efficacy success
 - **Safety success rates:**
 - Superior at 12 months
 - Non-inferior at 24 months

Risk - Benefit

Risk-Benefit Analysis

- **In assessing level surgical risks, it is important to**
 - **Focus on clinical impact of any adverse events that contribute to those risks**
 - **Balance those risks against functional impact**

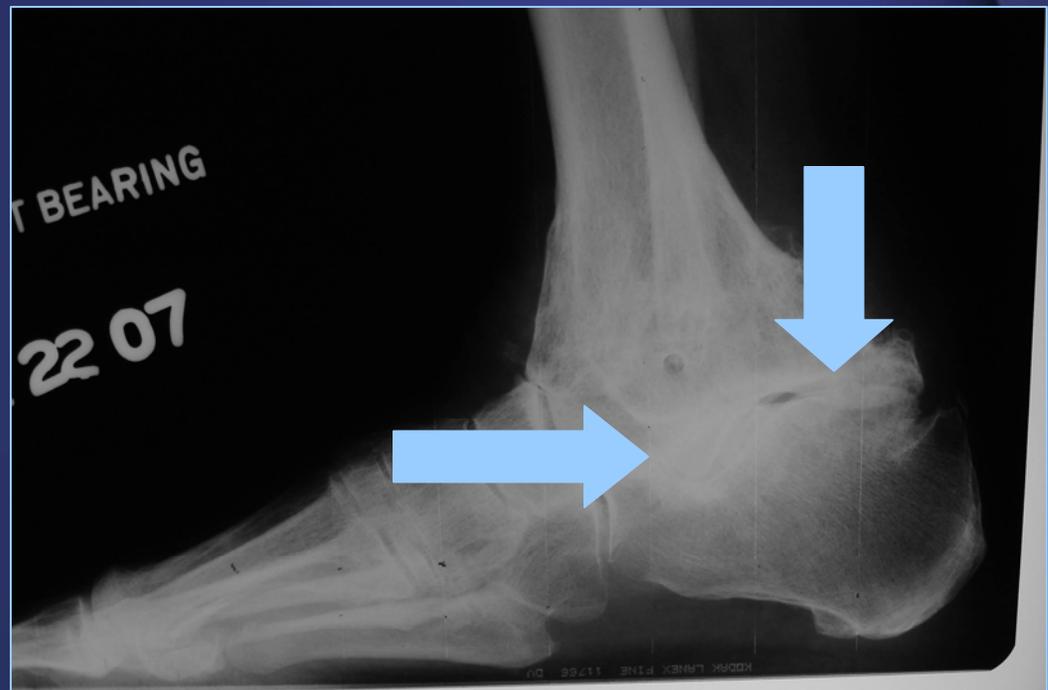
Risk-Benefit Analysis

- **Pivotal study suggests a higher adverse event rate than arthrodesis**
- **Majority of adverse events were minor and resolved without long-term consequences**
- **Decreasing adverse event rate in continued access suggests that rates decrease with refined surgical technique**
- **Both ankle arthrodesis and arthroplasty have clinically comparable and acceptable risks**

– Horton ER, RA Mann, J Mann. Presented at the American Orthopaedic Foot and Ankle Society 22nd Annual Summer Meeting. July 2006. La Jolla, Calif.

Risk-Benefit Analysis

- **Reduces progression of hindfoot arthritis**
 - Coster and Saltzman, JBJS 2001
 - Pyevich, JBJS 1998



Risk-Benefit Analysis

- **STAR has a number of important benefits**
 - Walk inclines and stairs without difficulty
 - Stand in comfort
 - Maintain near-normal mobility
 - Decrease secondary arthrosis
- **Multiple options for surgical revision**

Training Program

Andrew P. Greenberg

Learning Curve Analysis

- **Learning curve evaluated comparing rates of intraoperative fracture, major complications (wound/infection or bony changes), and surgical intervention:**
 - Pivotal study
 - First 15 patients of continued access study
 - Later continued access cases (>15)
- **Patients with completed 24 month follow-up were included in analysis of rate of surgical intervention or major complications**

Learning Curve Analysis

Event	Pivotal Study	Continued Access	
		1-15 patients	≥ 16 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%)

Learning Curve Analysis

	Pivotal Study	Continued Access Study	
	Pivotal Investigators	Pivotal Investigators	New Investigators
# 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%)

Learning Curve Analysis

- **Increased awareness and training on anterior surgical approach in USA practice provides new surgeons with an advantage**
 - Training/experience with Agility and other 2-part ankles
 - Training provided in residency/fellowship programs
- **For new surgeons, improved instrumentation and patient selection yield results similar to those of original investigators with substantial experience**

Overview of Training Program

- **Required certification for all surgeons before they are able to perform a procedure**
- **Training program consists of 1.5 days of didactic and cadaveric lab sections**
- **Each trained surgeon will be provided**
 - **Surgical video**
 - **Procedure manual**
 - **Implant and instrument manual**
 - **Contact information for company and at least one instructor**

Outline for Training Program

- **Lecture**
 - History of total ankle replacement
 - STAR Ankle device description and design rationale
 - STAR Ankle indications and contra-indications: How to select the right patient
 - Warning, precautions and surgical pitfalls
 - Adverse events: How to avoid and manage
 - Recent changes to instrumentation and technique

Outline for Training Program (cont'd)

- **STAR surgical procedure video review**
- **STAR surgical procedure cadaver lab**
- **Lecture**
 - Patient instructions and post surgery follow-up regime
 - Revision and reoperation strategies when necessary
- **Certification testing**

Post-Approval Study

Objectives and Overview of Patients

1. To evaluate long-term revision or removal rate for STAR Ankle
 - Continued Access patients that consent to longer term follow-up
 - All patients in Continued Access study previously reported as failures are included

2. To assess learning curve of physicians who are initially treating patients with STAR Ankle
 - 125 newly-recruited patients
 - 5 sites that did not participate in IDE studies
 - Potentially slow to enroll as low volume procedure

Principal Endpoints

1. Long-term revision or removal rate for STAR Ankle
 - Revision or removal rate of STAR Ankle at 4 years post surgery with confirmation at 6 and 8 years

2. Learning curve of physicians who are initially treating patients with STAR Ankle
 - Major complications within 12 months post surgery
 - Revisions, removals, or reoperations
 - Wound problems requiring surgical intervention
 - Infections requiring surgical intervention
 - Perioperative fractures that require surgical intervention and fixation

No Need for Control Group

- **Principal endpoints of study (long-term revision and/or removal rate) of principal interest to surgeons and patients**
- **Arthrodesis rates are well-known and do not change with > 12 months follow-up; well described in literature**

Length of Study Follow-up

- 1. Long-term revision or removal rate for STAR Ankle**
 - 6 weeks, 1 year, 2 years, 4 years, 6 years, 8 years

- 2. Learning curve of physicians who are initially treating patients with STAR Ankle**
 - 6 weeks, 6 months, 1 year

Patient Follow-up and Compliance

- **8 year follow-up proposed**
- **Patient consent difficult to obtain with longer follow-up**
- **Historical long-term follow-up rate decreases with extended follow-up in orthopaedic studies**
- **Measures taken to improve follow-up rate**
 - **Visit window reminders**
 - **Patient cards with visit windows**

All Study Visit Follow-up Evaluations

- **Assessment of operative site adverse events**
- **Clinical examination**
- **Radiographs**
- **Patient Evaluations**
 - **Buechel-Pappas score**
 - **Pain Visual Analog Scale (VAS) - 100mm**
 - **Quality of Life (SF-36)**
 - **AOFAS**

Thank you

