Link Orthopaedics Scandinavian Total Ankle Replacement System (STAR Ankle) PMA – P050050

Orthopedic and Rehabilitation Devices Advisory Panel Meeting April 24, 2007

FDA:

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Outline

- Reasons for Panel Meeting
- Device Description
- Pre-Clinical Testing
- Study Design
- Clinical Results
- Statistical Overview
- Post-Approval Study
- Panel Questions

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Reasons for Panel Meeting

- First-of-a-kind non-constrained ankle device
- Pre-Clinical Issue
  - Adequacy of wear testing as a surrogate long-term endpoint
- Clinical Issues
  - Definition of safety endpoint criteria
  - Continued access follow-up and modifications
  - Surgical technique
  - Learning curve determination

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STAR Ankle Device Description

- Non-constrained, mobile-bearing ankle system
- Tibial component
  - CoCr alloy w/ cpTi coating
  - Non-cemented
- Mobile bearing
  - UHMWPE (not crosslinked)
  - 5 sizes (6 – 10 mm nominal thickness)
- Talar component
  - CoCr alloy w/ cpTi coating
  - Non-cemented

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Pre-Clinical Testing

- Wear testing was performed using a joint simulator
- Worst-case sizes
- Compression force was held relatively constant at 3000 N
  - 163 lbs x (4.137x body weight)
- All samples survived 10 million cycles without failure

Pre-Clinical Testing

- Loads used for wear testing may not be worst case
- 250 lbs x (5.500x body weight) ~ 6116 N

versus

- 163 lbs x (4.137x body weight) ~ 3000 N

- Fractures of the mobile bearing reported in literature and in applicant's post-hoc explant analysis

Indications for Use

The applicant has proposed the following Indications for Use:

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

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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
- 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

Investigational Study Design

Approved IDE Protocol

- Conditionally approved June 2000
- Prospective, multicenter, non-randomized, concurrently controlled clinical study
- Investigational device group
- Control group - arthrodesis

Study Endpoint Assessments

- 1.) Primary Efficacy Endpoint
  - Mean total Buechel-Pappas Scale (BP) score measured at 12 months and 24 months.
  - 100 point scale based on pain (40 points), function (40 points), range of motion (15 points), deformity (5 points)
  - Success defined as a minimum 40 point increase from baseline

- Modifications
  - STAR Ankle has natural ROM advantage over arthrodesis (15 points in the BP score)
  - FDA requested evaluation excluding ROM (not a validated method)
  - AOFAS scale added to CA cohort

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Study Endpoint Assessments

- 2.) Primary Safety Endpoint
  - No device failures, revisions, removals
  - Radiographic success (no radiolucency, tilting or migration > 4 mm)
  - No major complications
- Modifications to the original radiographic success analysis

Overall Patient Success

- ≥ 40 point improvement in total BP score
- No device failures, revisions, or removals
- Radiographic success, defined as no radiographic evidence of loosening or migration in the STAR ankle group and no radiographic evidence of non-union, delayed union , or malunion in the control arthrodesis group
- No major complications, defined as lack of significant infection, no delayed would healing requiring surgical intervention, no significant post-op fractures of adjacent bones and no significant bony changes of adjacent bones requiring surgical intervention

Changes to IDE Approved Pivotal Analyses – Radiographic Success Assessment

- **Not Carrying Forward Radiographic Failures**
  - **Original: Failures at 6 or 12 months were carried forward as failures, irrespective of possible success at 24 months**
  - **Revised: Applicant identified 7 patients who were radiographic successes at 24 months that had earlier failures carried forward**

- **Counting these 7 patients as successes increases success rate, but 15% non-inferiority margin delta was not met.**

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Changes to IDE Approved Pivotal Analyses – Radiographic Success Assessment

- Reassessment in Radiographic Success Criteria
  - Original: Any radiolucency, tilting or migration > 4 mm →failure
  - Revised: Adding patients with radiographic failures at 24 months but showing clinical success at 48 months and no apparent progression of radiographic failure
  - 5 patients now considered successes

- Counting these 5 patients as successes along with the 7 previous patients increases the safety success rate → 15% non-inferiority margin delta was met

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Patient Cohorts

I – Investigational
C – Control

All Enrolled
627 I subjects
66 C subjects

Continued Access Group
- Follow-up at 24 months: 65.9% (211/320)
- Patients w/ x-ray review: 53.3% (80/150)

Pivotal Study

Compassionate Use
16 procedures

Continued Access (unilateral)

448 subjects

Bilateral
16 I subjects
27 I procedures

Unilateral
158 I subjects
66 C subjects

Pivotal Study Unilateral Group:
- Complete follow-up at 24 Months: 96.7% (145/150)
- Control follow-up at 24 Months: 77.4% (48/62)

Link Scandinavian Total Ankle Replacement System PMA - P050050 Clinical Results:

FDA Presenter:
Neven A. Popovic, D.V.M., M.D., Ph.D.

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Clinical Results – Overview

- Operative Data
- Primary Efficacy Endpoint
- Composite Safety Endpoint
- Overall Patient Success
- Secondary Efficacy Endpoints

Operative Data
Pivotal Study

- Similarity among the controls and the STAR patients in:
  - Anesthesia time
  - Surgery time
  - Length of hospital stay
- Local anesthesia use greater in controls
  (56.1% vs. 28.7% for STAR)
- Estimated blood loss less in STAR
  (53 cc vs. 75cc in Controls)

Operative data (Cont.)
Continued Access (CA) Study

- Similar surgical blood loss as the pivotal study group
- Fewer patients operated under general anesthesia (16.5% vs. 37.6% for the STAR pivotal group)
- Decrease length of hospital stay for CA patients (2.8 days vs. 3.1 days for the pivotal STAR group)

Primary Efficacy Endpoint Criteria

- Total Buechel-Pappas Scale (BP) score measured at 12 and 24 months
- For Individual Patient Efficacy success defined as≥40 point increase in BP score
- BP score is based on a 100 point scale consisting of subscale for pain (40 pts), function (40 pts), range of motion (15 pts) and deformity (5 pts)

Individual Patient Efficacy Success Rates at 12 and 24 Months

		Control			STAR			Difference in Success Rates, STAR-Control
Follow-up Visit	Patient Population	n	N	%	n	N	%	
Month 12	Completers	7	53	13.2 %	84	143	58.7%	45.5%
Month 24	Completers	7	47	14.9%	83	142	58.5%	43.6%

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Primary Efficacy Endpoint Results: Mean BP Scores at 24 Months for Completers

	Control (N=47)		STAR (N=142)	
	Mean	**Change from Baseline**	**Mean**	**Change from Baseline**
BP Score with ROM	69.7	26.3	81.6	40.5
BP Score Without ROM	66.4	30.0	69.2	36.9

Composite Safety Endpoint Criteria

- Composite safety endpoint derived from:
  - No evidence of device failures, revisions or removals
  - Radiographic success
  - No evidence of major complications

Major Complications

- Defined as:
  - Significant infection
  - Delayed wound healing requiring surgical intervention
  - Post-operative fractures of adjacent bones
  - Significant bony changes of adjacent bones requiring surgical intervention

Adverse Events up to 24 Months (Pivotal Study)

Adverse Events (n)	Control, N=66	STAR, N=158
	n/N	n/N
bone fracture*	2/66 (3%)	28/158 (17.7%)
bony changes (e.g. osteolysis, exostosis or osteophyte formation)*	0 (0%)	12/158 (7.6%)
nerve injury (e.g. numbness, decreased sensation, known sacrificed nerve)*	5/66 (7.6%)	32/158 (20.3%)
wound problem (e.g. wound dehiscence, delayed wound healing, skin necrosis)*	4/66 (6.1%)	32/158 (20.3%)
Surgical intervention	11/66 (16.7%)	34/158 (21.5)
Major complications	1/66 (1.5%)	14/158 (8.9%)
*The difference is statistically significant at 0.05 level without multiplicity adjustment		

Summary of Surgical Interventions Pivotal Study

	Control	STAR
Total number of Patients (N)	66	158
	n/N	n/N
Patients with Surgical Interventions (n)	**11/66 (16.7%)**	**34/158 (21.5%)**
Intervention Type		
Revision	4/66 (6.1%)	17/158 (10.8%)
Removal	7/66 (10.6%)	6/158 (3.8%)
Re-operation	2/66 (3%)	9/158 (5.7%)
Minor Operative Site Procedures	7/66 (10.6%)	10/158 (6.3%)
Hardware Removal*	**7/66 (10.6%)**	**1/158 (0.6%)**
Excision Exostosis	0 (0%)	5/158 (3.2%)

* The difference is statistically significant at 0.05 level without multiplicity adjustment

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Summary of Surgical Interventions Pivotal Study (Cont.)

	Control	STAR
Total number of Patients (N)	66	158
	n/N	n/N
Patients with Surgical Interventions (n)	**11/66 (16.7%)**	**34/158 (21.5%)**
Major Operative Site Procedures*	**3/66 (4.5%)**	**23/158 (14.6%)**
Component removal*	**0 (0%)**	**17/158 (10.8%)**
Fracture fixation (ORIF)	0 (0%)	2/158 (1.3%)
Repair nonunion	2/66 (3%)	0 (0%)
Major Procedures Not Device Related (hardware removal, fusion adjacent joint)	4/66 (6.1%)	4/158 (2.5%)
*The difference is statistically significant at 0.05 level without multiplicity adjustment		

STAR Surgical Interventions Pivotal Study (Cont)

	n	n/N*
Patients with Surgical Interventions	34	21.5%
Mobile bearing Removed	17	10.8%
Mobile bearing Replaced	15	9.5%
Talar Component Removed	7	4.4%
Talar Component Replaced	4	2.5%
Tibial Component Removed	7	4.4%
Tibial Component Replaced	3	1.9%

* N = 158 (number of patients)

Surgical Technique

- Instrumentation changes
- Surgical technique changes
  - General use of small talar components, allowing for less bone resection
  - Use of thicker mobile bearings to reduce wear
  - Use of hand retractors instead of self-retaining retractors
- Applicant purports these modifications have contributed to a decrease in adverse events

Comparison of Adverse Events in Control, Pivotal and Continued Access Groups at 24 Months

	Pivotal Study		Continued Access Arm
Adverse Events (n)	Control (N=66)	STAR (N=158)	STAR (N=352)
	n/N	n/N	n/N
bone fracture*	2 (3.0%)	28 (17.7%)	37 (10.5%)
pain*	32 (48.5%)	69 (43.7%)	115 (32.7%)
nerve injury	5 (7.6%)	32 (20.3%)	75 (21.3%)
wound problem	4 (6.1%)	32 (20.3%)	65 (18.5%)
surgical intervention*	11 (16.7%)	34 (21.5%)	26 (7.4%)
revision or removal* (device/hardware)	10 (15.25%)	21 (13.3%)	12 (3.4%)
other intervention*	3 (4.5%)	19 (12%)	15 (4.3%)
major complication	1 (1.5%)	14 (8.9%)	17 (4.8%)

* The difference with the STAR Pivotal Arm is statistically significant at 0.05 level without multiplicity adjustment

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STAR Radiographic Data, Accounting of Evaluated Patients

Evaluation Timepoint	Number of Patients with Radiographic Evaluations/Total Rad. Evaluations*	Number of Radiographic Evaluations/Total Patients**
6 months	148/151* (98.01%)	148/158 (93.67%)
12 months	134/151 (88.74%)	134/158 (84.81%)
24 months	141/151 (93.37%)	141/158 (89. 24%)

*Total number of patients with any radiographic evaluation=151

**Total number of surgical patients=158

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Radiographic Success Definition, Original IDE Criteria

- Defined as lack of radiographic evidence of loosening or migration in the STAR ankle group and no radiographic evidence of non-union, delayed union or malunion in the arthrodesis group

- Radiographic failures at 6 and 12 months were carried forward as failures irrespective of possible radiographic success at 24 months

Radiographic Success Definition, Sponsor Proposed Changes of Data Analysis (03/2007)

- Patients with radiographic failures at 6 or 12 months but meeting the radiographic success criteria at 24 months were not considered failures (7 patients involved).

- Patients with radiographic failure at 24 months were to be considered radiographic success based on the clinical outcomes at 48 months and an apparent lack of progression of radiographic findings at 48 months (5 patients involved).

Radiographic Failure using Original Radiographic Analysis

	Failure on X-ray (STAR)	Failure on X-ray (Control)
Evaluation Timepoint	n/N*	n/N*
6 months	4/148 (2.70%)	6/63 (9.5%)
12 months	8/134 (5.97%)	4/52 (7.7%)
24 months	13/141 (9.22%)	1/45 (2.2%)
n/N*= number of patients with radiographic failure (n) over Number of patients with radiographic evaluations (N)		

Radiographic Failure, Time of Initial Radiographic Failure (STAR)

Evaluation Timepoint	Initial Failure on X-ray (STAR)	Total Failure on X-ray at Specified Time
6 months	4/148 (2.70%)	4/148 (2.70%)
12 months	6/134 (4.47%)	8/134 (5.97%)
24 months	10/141 (7.09%)	13/141 (9.22%)*

* One (1) failure noted at 12 months - no additional X-rays obtained at 24 months – radiographic status at 24 months unknown

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Radiographic Success Rates for Completers at 24 Months

	Control	STAR
Original Analysis Criteria	44/45 (97.8%)	120/141 (85.11%)
Revised Analysis Criteria – not carrying forward prior X-ray failures (additional 7 STAR patients)	N/A	127/141 (90.07%)
Revised Analysis Criteria – not carrying forward prior X ray failures (additional 7 STAR patients) **AND** adding patients with radiographic failures at 24 months but showing clinical success at 48 months and no apparent progression of radiographic failure (additional 5 STAR patients)	N/A	132/141 (93.62%)

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Overall Patient Success

Defined as:

- ≥ 40 point improvement in total BP score
- No device failures, revisions or removals
- Radiographic success
- No major complication

Overall Patient Success Rates for Completers at 24 Months

	Pivotal Study	
Success at 24 months	**Control**	**STAR**
Original Radiographic Analysis Criteria	43/52 (82.7%)	101/142 (71.1%)
Revised Radiographic Analysis Criteria – not carrying forward prior X-ray failures (additional 7 STAR patients)	43/52 (82.7%)	108/142 (76.1%)
Revised Radiographic Analysis Criteria – not carrying forward prior X-ray failures (additional 7 STAR patients) **AND** adding patients with radiographic failures at 24 months but showing clinical success at 48 months and no apparent progression of radiographic failure (additional 5 STAR patients)	43/52 (82.7%)	113/142 (79.6%)

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Secondary Endpoints

Consist of:

- BP subscales of function and range of motion
- Improvement in total BP score of $\geq$40 points
- Pain visual analog scale (VAS, 100 mm scale)
- Patient satisfaction (Coughlin scale)
- Quality of life (SF-36)
- Medication use

Secondary Efficacy Endpoints Results at 24 Months

- **BP subscale for Function and ROM**
  - STAR patients have higher function score (13.4 vs. 9.7)
  - STAR patients have increase in ROM over the baseline (2.5 vs. 3.6)
- **Total BP Scale**
  - Similar between STAR and control groups
- **Pain Visual Analog Scale (VAS)**
  - STAR patients have slightly higher VAS values than controls (51.8 vs. 44.6)
- **Patient Satisfaction, Quality of Life (SF-36) and Medication Usage**
  - Similar between the STAR and the control groups

The Learning Curve

- Compared the 1st 15 patients of the pivotal study to the 1st 15 patients in the CA study and later CA cases
- Compared 3 new CA investigators with pivotal study and CA investigators
- Role of additional surgeon training, modification of surgical technique
- Learning curve not established but suggested as 15 patients by the applicant

P050050 S.T.A.R.
Statistical Overview

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April 24, 2007

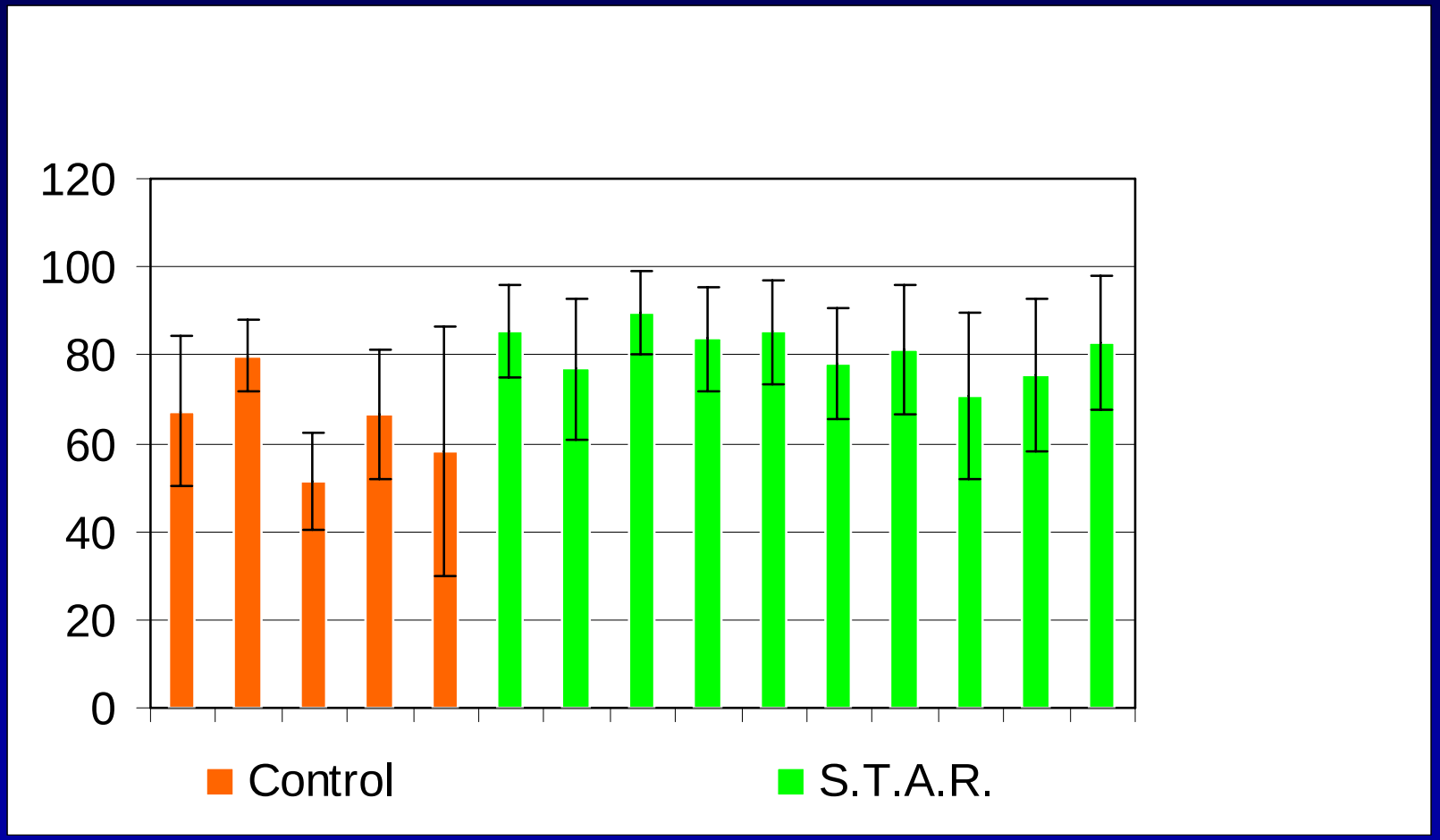
Outline

- Pivotal Study Design and Conduct
- Comparability of STAR and Control Patients
- Results on Primary Effectiveness Endpoint
- Results on Primary Safety Endpoint
- Meta-analysis on Arthrodesis Literature
- Summary

Pivotal Study Design

- Non-randomized, concurrent control
- Ten sites enrolled exclusively STAR patients, five sites enrolled exclusively arthrodesis controls
- Treatment effect confounded by site effect

Pivotal Study 24-Month BP Score by Site



Pivotal Study Design and Conduct

- Sample size estimation:
  - 158 STAR patients, 79 arthrodesis controls
  - Based on individual patient safety endpoint
- Actual enrolled patients:
  - 158 STAR patients, 66 arthrodesis controls (including 3 not due for 24-month visit)
  - Incomplete study

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Pivotal Study Patient Follow-up at 24 Months

	Control	STAR
Enrolled	66	158
Not Overdue	3	0
Failures	0	2
Deaths	1	4
Transfers	0	2
Overdue / Lost to follow-up	14 (21%)	5 (3%)
Actual *	48 (71%)	145 (90%)

* Number of patients with any 24-month follow-up data

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Patient Demographics and Baseline Characteristics

	Control (N=66)	STAR Pivotal (N=158)	P-value *
Age			0.004
Mean (SD)	57.1 (12.3)	62.7 (12.6)	
Primary Diagnosis			0.054
Primary Arthrosis	19 (28.8%)	62 (39.2%)	
Posttraumatic Arthrosis	43 (65.2%)	76 (48.1%)	
Rheumatoid Arthrosis	4 (6.1%)	20 (12.7%)	
Baseline Total BP Scores			0.058
Mean (SD)	43.0 (8.8)	40.8 (7.4)	
Baseline Pain VAS Scores			0.073
Mean (SD)	65.8 (19)	71.1 (17)	

* Not adjusted for multiplicity

Propensity Score Quintiles

Propensity Score Quintile[1]	Total Patients[2]	
	Control	STAR
1	0	43
2	5	39
3	11	33
4	17	27
5	29	15

1. Propensity score model included: adequate ligament support, age, BMI, diagnosis, functional difficulties, general condition, smoker, baseline total BP and VAS.
2. Total patients with covariate data available.

Primary Effectiveness Endpoint

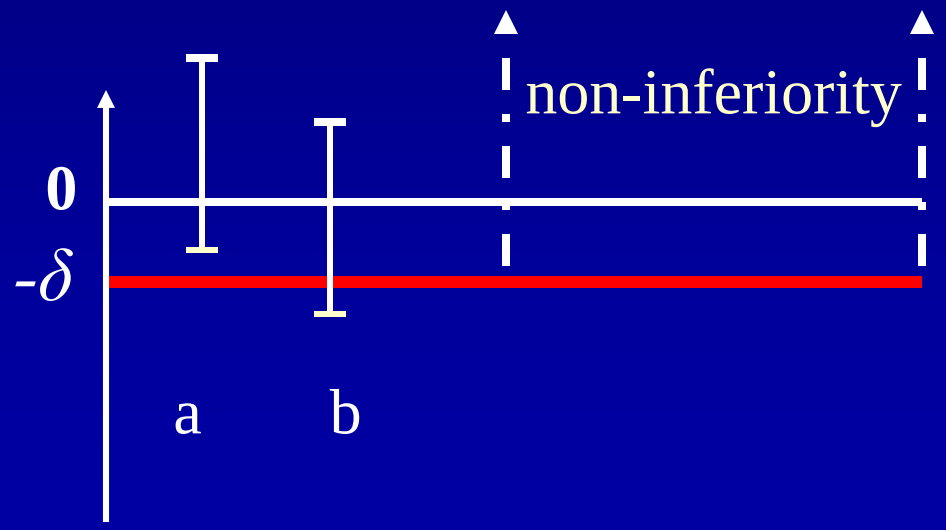
- The primary effectiveness endpoint is the Buechel-Pappas score (0-100)
- Pre-specified non-inferiority margin 10 points
- Non-inferiority is not based on the observed difference, but on the lower limit of the one-sided 95% confidence interval on the observed difference

Non-inferiority

H_0: $BP_s - BP_c \leq -\delta$ STAR *is worse than* Control *by more than* δ

H_1: $BP_s - BP_c > -\delta$ STAR *is at least as good as* Control

If the lower bound of one-sided 95% CI ($BP_s - BP_c$) > $-\delta$,
→ claim non-inferiority



Primary Endpoint Analyses – B-P Scores at 24 Month

Patient population (Covariate Adjustment*)	Missing Data Imputations	Control B-P Score	STAR B-P Score	Difference (STAR – Control)	LB of One-sided 95% CI**
Per Protocol (Unadjusted)	No Imputation	70.1	81.7	11.6	7.1
Per Protocol (Adjusted)	No Imputation	N.A.	N.A.	10.6	6.1
Intent-to-treat (Adjusted)	LOCF	N.A.	N.A.	13.6	9.7
Intent-to-treat (Adjusted)	Multiple Imputation	N.A.	N.A.	12.0	7.0

*Adjusted for age, primary diagnosis and baseline BP scores

** Non-inferiority is established if the lower bound of the 95% CI is greater than -10

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Primary Endpoint Analyses – B-P Scores Excluding ROM at 24 Month

Patient population (Covariate Adjustment*)	Missing Data Imputations	Control Modified B-P Score	STAR Modified B-P Score	Difference (STAR – Control)	LB of One-sided 95% CI**
Per Protocol (Unadjusted)	No Imputation	67.9	69.3	1.6	-2.7
Per Protocol (Adjusted)	No Imputation	N.A.	N.A.	1.5	-2.8
Intent-to-treat (Adjusted)	LOCF	N.A.	N.A.	5.4	1.7
Intent-to-treat (Adjusted)	Multiple Imputation	N.A.	N.A.	4.4	-0.6

*Adjusted for age, primary diagnosis and baseline BP scores

** Non-inferiority is established if the lower bound of the 95% CI is greater than -10

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Primary Safety Endpoint

- The primary safety endpoint is patient safety success, defined as
  - No device failures, revisions or removals
  - No radiographic failures
  - No major complications
- Pre-specified non-inferiority margin 15%
- Non-inferiority claim is not based on the observed difference, but on the lower limit of the one-sided 95% confidence interval on the observed difference

Patient Safety Success at 24 Months (Original Radiographic Interpretations)

Patient Population	Control Success Rate	STAR Success Rate	Difference (STAR – Control)	LB of One-sided 95% CI for Difference
Per Protocol	33/40 (83%)	88/126 (70%)	-13%	-25%
“Completers”	43/52 (83%)	101/142 (71%)	-12%	-22%
ITT Single Imputation	55/66 (83%)	112/158 (71%)	-12%	-22%

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Patient Safety Success at 24 Months
(Compare Original and Modified Radiographic Interpretations in "Completers" Population)

Radiographic Interpretations	Control Safety Success Rate	STAR Safety Success Rate	Difference (STAR – Control)	LB of One-sided 95% CI for Difference[3]
Original interpretation	43/52 (82.7%)	101/142 (71.1%)	-11.6%	-22.2%
Modified Interpretation #1[1]	43/52 (82.7%)	108/142 (76.1%)	-6.6%	-17.1%
Modified Interpretation #2[2]	43/52 (82.7%)	113/142 (79.6%)	-3.1%	-13.4%

1. Seven (7) STAR patients with early radiographic failures but 24-month radiographic successes were treated as radiographic successes.
2. Five (5) additional STAR patients with certain radiographic findings were treated as radiographic successes.
3. The 15% non-inferiority margin is met if the lower bound of the one-sided 95% CI is greater than -15%.

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Patient Safety Success at 24 Months for the Pivotal Study and Continued Access Study (Original Radiographic Interpretations)

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

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

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Meta-analysis on Arthrodesis

- Purpose: To supplement the safety data of control patients
- Forty-two (42) articles (after 1978), 1264 patients reviewed
- Twelve (12) articles (1983-1999), 413 patients included
- Sponsor found complication rates comparable with pivotal study
- Selection bias difficult to assess

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Summary

- Non-randomized pivotal study
  - Treatment effect confounded with site effect
- Control enrollment incomplete, poor follow-up
- Comparability of STAR and control population questionable

Summary (continued)

- Noninferiority may be shown in primary effectiveness endpoint
- Noninferiority in primary safety endpoint depends on radiographic interpretations
- Continued access patients difficult to evaluate due to incomplete follow-up
- Post-hoc meta-analysis difficult to assess selection bias

STAR Ankle Post-approval Study (PAS)

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Orthopedic and Rehabilitation Devices Panel Meeting
April 24, 2007

Reminder

- The discussion of a Post-Approval Study (PAS) prior to a formal recommendation on the approvability of this PMA should not be interpreted to mean that FDA is suggesting the Panel find the device approvable.
- The plan to conduct a PAS does not decrease the threshold of evidence required to find the device approvable.
- The premarket data submitted to the Agency and discussed today must stand on its own in demonstrating a reasonable assurance of safety and effectiveness in order for the device to be found approvable.

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PAS General Principles

- Objective is to evaluate device performance and potential device-related problems in a broader population over an extended period of time after premarket establishment of reasonable device safety and effectiveness

- Post-approval studies **should not** be used to evaluate unresolved issues from the premarket phase that are important to the initial establishment of device safety and effectiveness.

Post-Approval Study Uses

- Gather postmarket information
  - Longer-term device performance
  - Community performance (clinicians & patients)
  - Effectiveness of training programs
  - Sub-group performance
  - Real world experience & rare adverse events
- Address Panel recommendations

Overview of Applicant's PAS Plan

- Two-component prospective cohort study, without control group
  - A long-term follow-up component
  - A short-term physician learning curve component

Overview of Applicant's PAS Plan (Cont.)

	Long-term Follow-up	Physician Learning Curve
Population	STAR Ankle patients from Continued Access Study	New surgeons (5) and STAR Ankle patients (125)
Data Collection	48, 72 and 96 months post-operation	baseline, 6 weeks, 6 and 12 months post-operation.
Primary Outcome	Device revision/removal	Complications
Secondary Outcomes	Total B-P score, AOFAS Score Pain Visual Analog (VAS), Quality of life (SF-36)	
Radiographic assessment	By treating surgeons	

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Assessment of Applicant's PAS Study Type

- Study is not hypothesis-driven, even for the subgroup analysis of STAR Ankle patients

- Hypothesis-driven study is recommended:
  - Greater scientific rigor
  - Results would provide valid evidence for post-market action

Assessment of Applicant's PAS (cont.)
Study Control Group

- No control group
- Absence of control group significantly:
  - Diminishes scientific rigor
  - Limits the meaningful interpretation and utility of study results

Assessment of Applicant's PAS (cont.) New Enrollees

- The long-term follow-up component of the study only consists of patients from the CAS study
- Insufficient data on representativeness of patients and physicians in CAS study

- Limits:
  - the generalizability of the study results
  - the ability to examine device performance under actual conditions of use
  - the fulfillment of sample size requirements

Assessment of Applicant's PAS (cont.)
Loss to Follow-Up

- Significant losses to follow-up diminish the study validity.

Group	12-month	24-month
STAR Ankle (CAS)	84%	66%
Arthrodesis	85%	77%

- Plan to prevent excessive losses to follow-up:
  - Measures to prevent losses to follow-up
  - Compensatory measures when losses to follow-up occur

- A comprehensive plan to minimize loss to follow-up is absent

PAS Issues for Panel Discussion

1) Appropriate Control Group:

- STAR Ankle is proposed to be used as an alternative to Arthrodesis.
- Published data that compares the long-term outcomes of the two treatments is lacking[1].

1. Stengel D, et al. Arch Orthop Trauma Surg 2005;125:109-19.

PAS Issues for Panel Discussion

2) Radiographic Assessment:

- At 48, 72, and 96 months post-operation
- No involvement of independent radiologist
- No formal radiographic measurements will be obtained.

PAS Issues for Panel Discussion

3) The long-term outcome of STAR Ankle patients who have revision or convert to arthrodesis

- Published data (European study) indicated a revision rate for STAR Ankle of up to 30% (median= 52 months)[2].

- Data on the long-term outcome of these STAR Ankle patients are sparse.

2. Anderson T. et al J Bone Joint Surg Am 2003 85: 1321-29

PAS Issues for Panel Discussion

4) Appropriate length of follow-up and measures to control loss to follow-up

- Total ankle arthroplasty has many challenges which pose hurdles to achieving long-term success[3].

- The follow-up rates for STAR Ankle CAS and Arthrodesis control in PMA study were low.

3. Gill LH. Foot Ankle Int 2004;25:195-207.

Issues for Panel Discussion

5) The adequacy of the physician learning curve study

- Enroll 5 new surgeons,125 new patients, and follow 12 months post operation
- No sample size justification
- No sampling and recruitment plan

THANK YOU !

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