SUMMARY MINUTES

MEETING OF THE ORTHOPAEDIC AND REHABILITATION DEVICES PANEL

April 24, 2007

Hilton Washington DC North
Gaithersburg, MD

ORTHOPAEDIC AND REHABILITATION DEVICES PANEL
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Acting Chair:
John S. Kirkpatrick, MD
University of Florida

Standing Voting Members:
Stuart B. Goodman, MD, PhD
Stanford University

Kathleen J. Propert, ScD
University of Pennsylvania

Deputized Voting Members:
Michael B. Mayor, MD
Dartmouth Medical School

Glenn B. Pfeffer, MD
Cedars-Sinai Medical Center

Harry B. Skinner, MD, PhD
University of California, Irvine

Douglas G. Wright, MD
Trident Orthopaedic

Industry Representative:
Pamela W. Adams, MS, RAC, CQM
Etex Corporation, Inc.

Consumer Representative:
Connie Whittington, MSN, RN, ONC
Piedmont Hospital

Executive Secretary:
Ronald P. Jean, PhD

FDA Representative:
Mark N. Melkerson, MS

CALL TO ORDER

Chairman Kirkpatrick called the meeting to order at 8:10 a.m. and had the Panel Members introduce themselves. The meeting was held for the Panel to make a recommendation on PMA P050050 for the Link STAR Ankle Prosthesis, which was intended as a non-cemented implant to replace painful arthritic and/or severely deformed ankle due to rheumatoid arthritis, primary arthritis, or posttraumatic arthritis. He noted the presence of a quorum and that the Panel had received the appropriate training.

Executive Secretary Jean read the Appointment of Temporary Voting Members and Conflict of interest statements into the record. Drs. Mayor, Pfeffer, Skinner, and Wright were deputized as voting members. Dr. Kirkpatrick was appointed as the Acting Chairman. The Panel was found to be in compliance with federal ethics and conflict of interest laws, and no waivers were issued. The Panel participants were reminded to exclude themselves if the discussion raises a conflict of interest.

PANEL UPDATE

Dr. Jonette Foy gave an update on developments since the September 19, 2006 meeting. Panel meetings are tentatively scheduled for May 22-23, July 17-18, September 18-19, and November 13-14. Reclassification of intervertebral body fusion device, 888.3080, was under final review. The reclassification petition for non-invasive BGS (bone grown stimulator) for established non-union 1-2 level lumbar fusion had its comment period closed on April 17. The reclassification petition for metal on metal hip joint prosthesis was under active review.

Five orthopaedic guidance documents were under GGP review: for interbody fusion, cartilage, artificial disc, femoral stem, and OPC guidance for hip stems. FDA has put out two draft general guidance documents for comment. One is on modifications to devices subject to PMA and the PMA supplement decision-making process. The other addresses procedures for determining conflict of interest and eligibility in FDA advisory Committees. The agency released an FR notice on the goals associated with MDUFMA II, and a public meeting on the matter was held April 30, 2007.

DGRND has added three new staff members: Stephanie Bechtold, who is detailed to OSDB; John Lyons, MD, who is a part-time ORISE contractor; and Tara Shepard, who is working in OJDB. Chris Hack and Jonathan Pack are shared between ODE and OSB as collaborative reviewers.

OPEN PUBLIC HEARING

Chairman Kirkpatrick opened the floor for the first open public hearing. Dr. Jean read the public hearing statement into the record, urging speakers to disclose any conflicts of interest.

Dr. Lowell Gill, an orthopedic surgeon with a royalty agreement with KMI Integra, a competing device manufacturer, as well as relationships with Stelkast and Zimmer for total knees, disclosed that his travel expenses were paid by the Sponsor. He said that the Sponsor's project team is excellent. For the past nine years, he has held back from doing total ankle arthoplasty, due to concerns about the currently-available

prostheses. He has worked with companies on, observed ankle surgeries in many medical centers, and researched the literature. He demonstrated that triaxial motion reduces shear stress to the bone cement. Since bone strength decreases as distance from the joint increases, it is important to save bone, especially in patients with compromised bone. Conservative bone cuts must save the distal tibia, among other things.

Expanding surface area distributes force, and providing more than one plane of motion reduces stress on the interface. He said that that Sponsor's design increases surface area, allows motion on more than one plane, and employs a polyethylene insert to reduce shear stress. This design has been used extensively and successfully in Europe.

SPONSOR PRESENTATION

Andrew P. Greenberg, President of Link Orthopaedics, introduced the Sponsor's presenters. Link is the sister company of Waldemar Link in Germany and has been manufacturing joints since the mid '60s, including hip and knee replacements. The STAR (Scandinavian Total Ankle Replacement) Ankle has been marketed outside the US since 1990 and is the most widely-used total ankle replacement outside of the US. The device is a three-part ankle, while all approved ankles in the US are two-part, which are rarely used outside of the US.

Roger A. Mann, MD, a consultant to Link, gave a historical perspective on the device. Arthoplasty was introduced in the 1970s, but early complications eliminated it as a standard procedure. These were large, two-part implants requiring major bone resection and cementing. The amount of bone resected make revision difficult. The two-part ankle designs cleared by 510(k) and currently in use possess high interface stresses and incongruent metal to polyethylene articulation. They don't dissipate transverse rotation. It is difficult to balance the ligaments, and it is often used cementless, despite the labeling. Often these devices require large bone resection and an external fixator.

In Europe, there are multiple designs of three-part ankles in use. The Salto ankle entered the US market by attaching the polyethylene to the tibial component, making a two-part ankle. No US studies were completed on this design.

The STAR System requires minimal bone resection, 10 to 12 mm, which makes revision possible. It is unconstrained and non-cemented, with a porous ingrowth interface. The device consists of three components: the standard chromium alloy tibular component, a UHMWPE (ultra-high molecular weight polyethylene) mobile bearing, and the standard cobalt chromium alloy talar component. The mobile bearing design allows multiple planes of motion: dorsiflexion, plantarflexion, and transverse plane rotation, which reduces shear and torque forces that can loosen the bone-metal interface. The implant congruency is designed to decrease polyethylene wear and allow for near-normal ankle motion.

Charles L. Saltzman, MD, a consultant to and former grantee of the Sponsor, discussed pre-clinical testing. Mechanical testing showed minimal constraint in rotational, AP, and medial-lateral displacement modes. The load is shared with adjacent soft tissues, reducing stresses on the bone to implant interface.

The contact stress testing was first done with Fuji Film, which made possible an FEA model, which indicated that the internal and contact stresses were within tolerable limits. Thinner and unsupported or overhanging polyethylene had the highest stresses.

The testing protocol, developed by Orthopaedic Research Laboratory, simulated a worst case scenario. It used the smallest implant, thinnest poly component, poly overhang, heavy loads, and continuous loading for ten million cycles. No samples demonstrated functional failure, but the test did not test ligament imbalance, deformity, or transient high forces due to a traumatic event.

The explant analysis was requested after the PMA submission, so the data was collected post hoc. There were 35 mobile bearings available for analysis. The bearings were assessed for a grading of burnishing, abrasion, pitting, surface deformation, delamination, scratching, debris capture, and fracture. The most common findings were burnishing, scratching, pitting, and abrasion. Some of the damage may have occurred during removal. The fractures (two 9mm, one 10 mm, and one 7mm bearing, 4 in 600 patients) were all associated with joint imbalance, deformity, and trauma, not wear. Loss of polyethylene on the edge of a component occurred in 9 of the 35 retrieved bearings and was usually associated with contact from heterotropic bone. From the preclinical testing and expert analyses, the Sponsor concluded that suitability of STAR for implantation and long-lasting function was demonstrated. The testing conditions were appropriate to evaluate the mechanical stability of the device, and the adequacy of the testing was confirmed by long-term European clinical experience.

Dr. Saltzman next gave an overview of the clinical protocol. The study consisted of three parts: the pivotal study, the bilateral study, and the continued access (CA) study. The bilateral study was for safety alone, the other two for safety and efficacy. The objectives were to evaluate the efficacy and safety of STAR Ankle compared to ankle arthrodesis to treat patients with moderate or severe ankle pain, loss of mobility, and the loss of function due to arthritis. The study was designed as a multi-center clinical trial with 10 STAR Ankle sites and 5 arthrodesis sites; the 2:1 ratio of STAR to arthrodesis was designed. Historical controls were obtained through meta-analysis of the literature and provided further data. The concurrent control was arthrodesis, the current standard of care. External fixators were excluded to prevent confounding of the data.

The primary efficacy endpoint was the mean total Buechel-Pappas (BP) score. The composite safety endpoint was no major complications; no device failures, revisions, or removal; and a set of radiographic criteria—no evidence of loosening or migration in the STAR device, no evidence of non-union, delayed union, or malunion for the control. The sample size was calculated based on a non-inferiority study, with a 10-point efficacy delta and a 15 percent safety delta. To demonstrate efficacy, 24 STAR and 12 arthrodesis patients were needed, 134 STAR and 67 control patients for safety. Ultimately, 158 STAR patients enrolled and 66 arthrodesis.

The major inclusion criteria were primary ankle arthritis, post-traumatic arthritis, or rheumatoid arthritis; moderate or severe pain; loss of mobility and function in the ankle; and a failed trial of a foot or ankle orthosis or/and analgesic medication for three months; and a minimum of 6 months of conservative treatment. The major exclusion criteria included hindfoot malpositioning greater than 35 degrees, forefoot malalignment that 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, and neuromuscular impairment.

The post-op protocol for the control was a non-weight bearing cast for the first six weeks and a partial weight-bearing cast until full weigh bearing, usually a total of three to

four months in a cast. STAR patients were in a splint, immobilized and not weight bearing for two weeks. The patient then wore a 50 percent weight bearing cast from weeks 2 to week 4. From week 4 to 6, the patient wore a full weight bearing cast, and the patient was taken out of immobilization at the 6th week. There were visits at baseline, operation, 2-3 weeks, 6 weeks, 3 months, 6 months, 12 months, and 24 months. X-rays were performed at 6 months, 12 months, and 24 months.

The efficacy success endpoint was over 40 points of improvement on the 100 point BP scale. The BP Scale for total ankle replacement has 40 points for pain, 40 for function (among 5 subscales), and 20 for examination. This scale was used because it was used to evaluate arthoplasty patients.

Major complications were defined as surgical intervention for infection, wound problems, fracture, or bony changes. Radiographic review for the control was performed by the investigator, who evaluated fusion status. In STAR patients, radiographs were evaluated using a zonal analysis, and all radiographs were reviewed by one central reviewer. In the control, union was defined as over 50 percent bony bridging at 4 months or earlier. Delayed union was over 50 percent union at 4 to 6 months. Nonunion was less that 50 percent bony bridging after 6 months.

The purpose of the STAR radiographic review was to identify radiographic signs that predict failure, loosening. Two groups of patients were reclassified after the initial statistical report. The first group was reclassified due to inappropriate carrying forward of radiographic information. In the initial PMA analysis, patients who were not radiographic successes at 6 or 12 months were considered failures regardless of 24 month results. However, 7 patients who were not successes at 6 or 12 months met radiographic success at 24 months. Early radiographic findings were inappropriately assumed to predict long-term findings. The second group reclassified was 5 subjects who were initially classified as safety failures due to early settling of the implant. Since there were no further changes in the radiographs and the patients had satisfactory clinical results at 48 months, the patients should have been considered successful.

The bilateral study was a single-arm multi-center study of bilateral treatment in 21 patients in the other studies who presented with or developed bilateral disease. These patients were assessed for safety only. The CA study was a multi-center registry for three phases of 150 patients each at the same sites as in the pivotal study.

Many lessons were learned from the studies. At the onset, the anterior approach was less familiar than the lateral approach, but the anterior approach has become better-known and is now being taught. One problem with the anterior approach is susceptibility to wound problems due to thinner skin and less subcutaneous fat at the site. The incision runs down the center of an angiosome, affecting blood supply, and the procedure is susceptible to transient or permanent sensory loss on the medial dorsal aspect of the foot. Refinements in instrumentation, technique, patient selection, and post-op patient education have improved outcomes and reduced these effects.

Surgical modifications included lengthening of the incision, elimination of self-retaining retractors and skin staples, protecting the medial malleolus with K-wires, and implant selection. Generally, thicker polyethylene bearings and smaller talar components yield better results. Better capturing of the tibial saw blade caused decrease in bony nicks and incidence of fracture. Adjustable medial and lateral blocks facilitate precise device placement. The addition of talar trials and talar fin tamp helped assess bone preparation.

Patients were selected with an increased awareness of coronal plane deformity and exclusion of patients with peripheral neuropathy. Patients were instructed with an increased emphasis on compliance with recovery regimes.

Michael Coughlin, MD, a clinical investigator and consultant to Link, reported on the study results. He said enormous quantities of data were collected and excellent investigators from renowned institutions were sought out. Two equally talented groups were assembled, though the arthrodesis group was more experienced with their procedure and device. Since the control was standard of care, investigators and patients showed less compliance in follow-up, 81.5 percent at 12 months, 77.4 at 24, compared to 96.7 percent at 12 and 24 months. There was no significant difference in sex or race between the two groups. The STAR patients were significantly older (average 62.7 years, compared to 57.1). STAR patients had twice the control's rate of rheumatoid arthritis, which was associated with lower BP scores and higher complication rates. The two populations were comparable for gender, weight, and height, but the STAR patients were more debilitated at baseline. Despite the device being an unfamiliar surgical approach, operative characteristics (operative time, anesthesia time, estimated blood loss, and length of stay) were similar.

At the primary efficacy endpoint, mean BP score, STAR showed a significant improvement over the control, 80.7 points, compared to 65.9 at 12 months, 81.6 compared to 69.7 at 24 months. In a post-hoc analysis, the 15 point range of motion measure was excluded to account for arthoplasty's not claiming range of motion as an endpoint. Without crediting for range of motion, STAR still scored better than control, 68.3 points at 12 months and 69.2 at 24, compared to 63.6 at 12 months and 66.4 at 24 months. STAR's most substantial improvements were in deformity, function, and range of motion. Pain improvement was expected to be greater in the control group, but STAR improvement was better. Range of motion got worse after the control was implanted and significantly improved with STAR implantation. The goal was a 40 point improvement. The total mean improvement was 39.7 points at 12 months (23.3 in control), 40.5 points at 24 months (26.3 in control). With range of motion removed, STAR still shows more improvement than the control (35.9 vs. 28.3 at 12 months, 36.9 vs. 30 at 24). Improvement in BP function scores was significantly higher in the device compared to control. Significantly more patients in the STAR group than the control group showed an improvement of 40 points or more (58.7 percent at 12 months and 58.5 percent at 24 months, compared to 13.2 percent and 14.9 percent in the control).

Safety success was defined as no revisions or removals, no major complications, and radiographic success. In the original data, unadjusted for porous ingrowth and delayed settling, STAR had 80.1 percent safety success at 12 months, 71.1 percent at 24 months. Control had 87.7 percent at 12 months and 82.7 percent at 24 months. With review of the results, 12 patients were found to be successful at 24 months who were not previously counted as successes. When they are counted, STAR's safety success rate at 24 months is 79.6 percent and meets the 15 percent safety delta, which is not met without these revisions. It is also possible that the small size of the control group and its protocols exaggerate its safety. Investigator classifications could affect reporting of fusion failure rates, and 13.5 percent of control patients are not full weight bearing at 4 months. The overall success rates for both safety and efficacy at 24 months was 13.7

percent for the control, 45.1 percent for STAR before revision, 49.3 percent after. STAR is still superior when range of motion is excluded.

Adverse events were higher in the STAR group, some due to the criteria used, some due to the anterior approach. Some adverse events were not applicable to the control due to differences in procedure or expectation. Intraoperative fractures in the STAR group led to changes in technique, which ended the fractures. At 24 months, no STAR patients had major nerve injury, but nerve injury was higher in STAR due to superficial peroneal nerve injury. Bone fracture was higher, but the fractures were insignificant, reduced in the CA arm, and intrinsic to the control. Soft tissue edemas were transient and seen with early weight bearing. Wound problems were characteristic of the anterior approach and improved in the CA arm. Infection rates were lower in the STAR group, and delayed or non-union events did not apply to STAR.

These adverse events were rarely major complications. However, at 24 months there had been 33 surgical interventions (26 patients) in the STAR group, 9 in 7 patients in the control. Removal was more common in the control group. The pivotal STAR intervention rate was comparable to historical arthrodesis controls, and intervention rates decreased in the CA arm. Major complications were addressed by changes in surgical technique; STAR's safety profile was developed while the technique was being refined.

In December of 2005, FDA asked about radiographic review for CA patients. The Sponsor performed radiographic review on patients in the first arm of the controlled access study who had 24 month follow-up. Of 85 patients, 5 had incomplete radiographic data, due to the position of the ankle or poor x-rays. An independent radiographic review showed fewer failures in the review than in the pivotal study. In patients with radiographic reviews, there was 75.3 percent patient success, 84.3 percent efficacy success, and 88.9 percent safety success at 24 months. At 24 months, surgical intervention rates were cut in half, and all other adverse events are dramatically reduced.

Though the pivotal study suggested a higher adverse event rate than arthodesis, the majority of the events were minor, and all adverse events were reduced in the CA study. Both arthodesis and arthoplasty have clinically comparable and acceptable risks. STAR has additional benefits of making it easier for a patient to walk on inclines and stairs, stand in comfort, and maintain near-normal mobility. Additionally, it decreases secondary arthrosis and retains options for surgical revision.

Mr. Greenberg returned to talk about the training program. The Sponsor intends to run a training course for certification before a surgeon can perform the procedure. The day and a half class will have didactic and cadaveric lab sections and certification testing. Each surgeon will be given a surgical video, procedure manual, implant and instrument manual, and contact information for the company and an instructor.

The Sponsor also planned a post-approval study (PAS) evaluating long-term revision or removal rate for STAR Ankle at 4, 6, and 8 years and tracking the learning curve for surgeons implanting the device by following up for major complications and adverse events at 6 weeks, 6 months, and 12 months. Longer follow-up would be difficult and would harm recruitment.

Chairman Kirkpatrick opened the floor to questions from the Panel. Dr. Mayor asked about the handling of the polyethylene material. Dr. Coughlin said the material is made by Hoist in Europe and laser-cut by Link in the US. The implant is wrapped in plastic in a nitrogen environment and sterilized with radiation in the package.

Dr. Pfeffer asked how range of motion was determined. Dr. Coughlin said the goal was to use radiographs to compute range of motion, but that was too much radiation, so a goniometer was used. Dr. Pfeffer further asked how osteoporosis was determined. Dr. Coughlin said that osteopenia was determined by radiograph. When unsure, doctors administered a DEXA test. Patients who failed a DEXA test were excluded.

Dr. Wright asked about the arthrodesis group and fusion of the tibial/fibula joint. Dr. Mann said the lateral approach was used for ankle fusion in the control. The major advantage of the STAR Ankle is that it does not require fusion.

Chairman Kirkpatrick asked for the total bone resection. The total bone resected with STAR was 10 to 12 mm.

Dr. Pfeffer asked about the use of BMI and absolute weight in the initial study. Dr. Saltzman said that the device had a certain weight it could bear, and that was reflected in the exclusion criteria.

FDA PRESENTATION

Bryan Pinder, ME, lead reviewer, introduced the presentation. He addressed the reasons for the Panel meeting, the device description, the pre-clinical testing, and the study design. The meeting was held because the STAR Ankle is a Class III device, and the first of its kind, a non-constrained ankle device. There was a pre-clinical issue with the adequacy of the wear testing as a surrogate for a long-term endpoint, and there were clinical issues with the definition of the safety endpoint criteria, CA follow-up and modifications, surgical technique, and learning curve determination.

Pre-clinical testing was performed in a joint simulator using worst-case sizes and a relatively constant force of 3000 Newtons. All samples survived 10 million cycles. The Agency is concerned that the loading may not have represented a worst case scenario. The force applied to the joint was equivalent to 4.137 times a body weight of 163 lbs. However, the exclusion criteria allows patients up to 250 lbs, and ankle joint forces during normal gait can range from 2 to 5.5 times body weight. To show a worst case scenario, 6116 N should have been applied. Additionally, the testing did not mimic fractures reported in the literature.

The Sponsor's IDE protocol was approved in 2000. The study was designed to demonstrate noninferiority to arthrodesis, with safety and efficacy as primary endpoints. Since STAR patients would have a natural advantage over arthrodesis patients in range of motion, which makes up 15 points on the BP score, FDA requested evaluation excluding range of motion. The study safety endpoint assessments included radiographic success, and the Sponsor proposed modifications to the original radiographic analysis.

In the original PMA, radiographic failures at 6 and 12 months were carried forward as failures at 24 months. The Sponsor's post-hoc analysis identified 7 patients who were radiographic successes at 24 months but had been carried forward as failures due to earlier failures. Including these patients as successes increases the success rate, but the 15 percent noninferiority delta is still not met. This post-hoc analysis was not applied to the control group. Additionally, radiographic failure was defined as any radiolucency, tilting, or migration greater than 4 mm. The revised assessment allowed radiographic failures at 24 months to be called successes if they were clinically

successful at 48 months. This reassessment added 5 successful patients, and with the previous 7 patients added, the 15 percent non-inferiority margin was met.

Patient follow-up at 24 months was 96.7 percent in the STAR group, 77.4 percent in the control. The CA group had 65.9 percent follow-up, and 53.3 percent of patients received an x-ray review.

Neven A. Popovic, DVM, MD, PhD, addressed the clinical results. In the pivotal study, operative data shows similarity between the control and STAR arms in anesthesia time, surgery time, and length of hospital stay. The control arm had more local anesthetic use and blood loss. CA patients had blood loss similar to the pivotal study group, fewer patients under general anaesthesia, and a shortened hospital stay.

The primary efficacy endpoint was a 40 point or greater increase in BP score. At 24 months, 58 percent of STAR patients and 15 percent of control patients had shown a 40 point increase. The mean scores at 24 months showed an increase of 40.5 points, compared to the control. If range of motion points are excluded from the study, the control has a mean increase of 30 points, STAR 36.9 points.

Adverse events in the pivotal study demonstrated the pivotal arm had statistically significant increases in frequency of bone fractures, bony changes, adjacent nerve injury, and general bone problems. Additional surgical intervention was required in 21.5 percent of STAR patients and 16.7 percent of control patients. Major complications occurred in 8.9 percent of STAR patients, 1.5 percent of control patients. A number of adverse events and revisions were noted after 24 months, raising a question as to the adequacy of the follow-up. In the pivotal study, surgical interventions, such as reoperations and device revisions, were more common in STAR patients than in control; 10.8 percent of STAR patients and 6 percent of control patients has revisions. Control patients had more minor procedures, such as surgical hardware removal, but STAR patients had more major operative site procedures (14.6 percent, compared to 4.5 percent), most commonly device component removal. The most commonly-removed component was the mobile bearing.

Surgical technique changes were made over the course of the study, and the applicant said the changes led to reduced adverse events. The CA cohort showed a statistically significant decrease in bone fractures, post-surgical pain, and additional surgical interventions, but the decrease in major complications was not statistically significant. No appreciable reduction in local injury was noted, and bone fractures, nerve injury, bone problems, and major complications were still lower in the control group.

Radiographic success affects the safety endpoint and overall patient success. Of the 158 pivotal STAR patients, 151 had one or more radiographic evaluations at the timepoints. Not all patients with six month evaluations had 12 or 24 month evaluations. The Sponsor asked for changes in the radiographic analysis. However, 48 month clinical and radiographic data was not available for all patients. The original radiographic analysis shows STAR patients demonstrating increasing initial radiographic failure at each timepoint, while the control shows decreasing signs of initial failure. The revised analysis raises the radiographic success score from 85.11 percent to 93.62 percent, and this affects many composite outcomes, including the overall success rate.

In the secondary efficacy endpoints, the STAR cohort had higher function in range of motion. Patient satisfaction was essentially similar between the STAR and control populations. Surgical outcomes improved with experience, and development and modification of the procedure during the study is a significant variable. The Sponsor

suggests that the first 15 patients constitute the learning curve, but it is difficult to estimate a learning curve.

Jie Zhou, MS, gave a statistical overview of the submission. The pivotal study's nonrandomized design created confounding effects that are difficult to control for, such as site difference, which was present in both the control and STAR sites. The concurrent control group was weakened by poor follow-up and incomplete enrollments. Only 66 of the scheduled 79 control patients were enrolled. Technically, the pivotal study is not yet completed. Of those control patients enrolled, 21 percent were lost to follow-up, compared to 3 percent in the STAR group. If these patients were not lost purely at random, the results can be skewed.

The device and control groups have questionable comparability. The patients were not randomized, so the two groups are not balanced. Control patients were younger, had lower post-traumatic arthrosis, higher baseline BP scores, and lower baseline VAS (Pain Visual Analog) scores. A propensity score analysis showed that certain characteristics appeared only in STAR patients.

In the pivotal study, STAR patients showed noninferiority in the primary efficacy endpoint, but whether or not non-inferiority is demonstrated in safety depends on the interpretation of the radiographic data. Removing the range of motion advantage from the efficacy endpoint, noninferiority is still shown. The STAR population is less successful than the control at the safety endpoint, unless the radiographic evidence is revised as the Sponsor suggests in its post-hoc analysis, which was completed after seeing the results.

Follow-up is incomplete in the CA cohort. Since only 80 CA patients received independent radiographic reviews, it is difficult to compare them to the pivotal patients. The Sponsor's meta-analysis excludes many patients and articles. The Sponsor reviewed 42 articles, 1264 patients, but only included 12 articles, 413 patients. The complication rates were comparable to the control arm, but the post-hoc nature of the metaanalysis implies selection bias.

Cunlin Wang, MD, PhD, epidemiological reviewer, presented on the Sponsor's proposed PAS. He first made clear that discussion of a PAS did not imply that the FDA suggested approval and did not lower the threshold of evidence. The objective of the PAS was to evaluate device performance and potential problems in a broad population over an extended period of time.

The Applicant's plan was for a two-component prospective cohort study without a control group. It consisted of a long term follow-up component and a short-term physician learning curve component. The long-term follow-up will be in STAR Ankle patients from the CA study. Data will be collected at 48, 72, and 96 months post-operation, with the primary outcome of device revision or removal. The learning curve testing will look at 5 new surgeons and 125 STAR Ankle patients at baseline, 6 weeks, 6 months, and 12 months, with a primary outcome of complications. In both, the secondary outcomes will be BP score, AOFAS score, VAS, and Quality of life by SF-36. The treating surgeons will give the radiographic assessment.

FDA noted that the study was not hypothesis-driven and recommended a hypothesis for greater scientific rigor and so the results can provide valid evidence for post-market action. FDA also noted that the absence of a control group diminishes the rigor of the study and limits the meaningful interpretation and utility of the results. The

long term follow-up enrolls no new patients but uses patients from the CA study, on whom there is insufficient data on the representativeness of the patients and the surgeons. This limits the generalizability of the results, the applicability to actual conditions of use, and the odds of fulfilling the sample size requirements. Losses to follow-up diminish validity, and a plan is needed to prevent and compensate for losses to follow-up.

FDA suggested that the Panel discuss 5 issues: establishing an appropriate control group, how to handle radiographic assessment, the long-term outcome of STAR patients who have revision or convert to arthrodesis, the appropriate length of follow-up and measures to control loss, and the adequacy of the learning curve study.

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PANEL DELIBERATIONS

Dr. Pfeffer commented on the clinical evidence. He said that subtalar motion, which significantly effects outcome, was not measured but can be inferred by the total motion. The device and control groups should be similar in subtalar motion as well as other aspects, but the two populations were dissimilar in significant ways. The STAR group had 48.1 percent of their patients with post-traumatic arthritis. The control group had 65 percent. Control patients had had more surgeries at baseline. Most importantly, 53 percent of control patients had less than 14 degrees of motion, compared to 27.5 percent in the STAR group. He pointed out that, although there was no learning curve in the control group, that the 2.2 hour operation times implied that the fusions were very complicated. This again implied inferiority in the control group. Moderate or severe preoperative deformity was 41.8 percent in the pivotal group, compared to 12.2 percent in the CA group. Improvements attributed to improved technique, equipment, and ability may actually be due to better patient selection. He said these concerns may affect the final FDA recommendation.

Dr. Skinner said that the Panel was not given the original preclinical data but summaries of the data. The purpose of the preclinical study was to find potential problems prior to the studies. He agreed with the FDA that the device was not wear tested for a worst case scenario, and this was why the simulator results were not comparable to the clinical results. The testing should have used the maximum allowable patient weight and tested for misalignment during surgery. Second, the extremely thin polyethylene in the keel trough was a concern, since there were reported cases of fracture but no information on the location of the fractures. This was a likely location for high contact stresses. He said that the pressure-sensitive film data could have considered other scenarios. The FEA data made him think that the Sponsor should consider eliminating the smaller polyethylene components and the wires, which failed the wear test.

Severe malalignment requiring osteotomy was high, 2 percent, which implies that there was a higher rate of less severe malalignment, leading to wear and fracture. Further study would elucidate problems and lead to improved design.

Dr. Propert said that in a nonrandomized study the difference between the device arm and control arm should be controlled and measured. She said there were significant differences at baseline between the STAR and control arms. The differences suggested that there may be unmeasured covariates present, which cannot be fixed, since they are unmeasured. Second, since the different treatments were held at different sites, it is impossible to separate treatment effects from site effects. Third, the efficacy endpoint

was confusing, since the Sponsor presented the data simultaneously as a superiority study and a non-inferiority study. The efficacy endpoint was overpowered, since the sample size was based on safety. She pointed out that more severe baseline symptoms and disease severity in the STAR group did not favor the control group. It increased the potential for regression to the mean and made greater improvements possible.
She expressed concern that the safety endpoints had changed. When endpoints change, they should change uniformly and across the board. While it makes sense to use 24 month data over 12 month data if 24 month data is available, it does not make sense to compare 48 month data to 24 month data or use 24 month data to predict 48 month data.

The primary safety endpoint was, after the changes, just reaching the noninferiority margin, but there was no adjustment for the multiplicity of endpoints or for interim analysis. This adjustment would widen the confidence intervals and change the conclusions on the primary safety endpoint.

Chairman Kirkpatrick opened the floor for Panel discussion. Dr. Goodman asked for more information on osteoporosis, BMI, and worst-case-scenario wear testing. Dr. Saltzman said the Sponsor did not have plans for further wear testing. As for osteoporosis, there was no data on DEXA scans in total ankles, so the exclusion decision was based on hip DEXA scores. As for BMI and fractures, the Sponsor saw that weight did not correlate to the fractures that occurred, so that specification may change. Dr. Goodman asked who performed the procedures. Dr. Mann said that the surgeries were all performed by principle investigators, and cases were not handed over to fellows or residents. Dr. Goodman commented on the distinction between clinical and statistical significance.

Dr. Mayor asked about the FDA's recommendation for a hypothesis-driven PAS. Dr. Wang said that a hypothesis makes it possible to calculate a sample size and detect significance. The hypothesis defines what data is collected, while an observational study can only provide post-hoc analysis. The FDA's primary concern was revision rates, so the hypothesis would be that the revision rates are not inferior to the control group.

Dr. Pfeffer noted the complexity of including or excluding range of motion data. He asked about converting a total ankle to an arthodesis and its effect of subtalar motion. Dr. Coughlin said that the literature shows high success rates in revisions. The less bone removed in the earlier procedure, the better the results. Dr. Pfeffer further asked for the Sponsor's guidelines on deformity. Dr. Mann said that deformity and patient selection was part of the learning curve. More than 10 degrees of deformity would contraindicate the procedure. The important thing is to have plantargrade foot. Diabetic patients are contraindicated because they develop neuropathies, which can weaken bones. Dr. Pfeffer asked about testing the device to failure to determine its strength. Dr. Saltzman said of the four fractures, two of the patients were in major trauma and one had 35 degrees of deformity. All patients with fracture had deformity and ligamentous instability. Most of these patients had the bearing replaced. Testing to failure by the causes of failure is difficult to model. Dr. Skinner agreed that a static load test to failure would not help.

Dr. Skinner asked if surgeon skill had anything to do with why US and European data did not match. Dr. Coughlin said the US study, in part, was to determine whether or not the non-US data was trustworthy.

Chairman Kirkpatrick asked about prospective analysis of the deformity issue. Dr. Saltzman said that there had not been a retrospective analysis covering deformity,

only in patients with failures. Chairman Kirkpatrick commented on the importance of developing a hypothesis at the beginning, sticking to the study protocols, and not mixing post-hoc analysis with the prospective study presentation.

The Panel presented many questions for the Sponsor to address. Dr. Coughlin first addressed Dr. Skinner's question about the European study by Dr. Anderson. The US study was the first with an arthodesis control. The Anderson study shows 12 failures in 51 cases and does not note exclusion or inclusion criteria. He had unique instrumentation and did not note trial device sizes. The US trial was much better run and better recorded. He added that operative time does not indicate difficulty or severity.

Dr. Tom Clanton, a Link consultant, said the meta-analysis was not a result of cherry-picking articles. The original review of ankle arthritis literature went back to 1945 and included 73 articles with an average overall complication rate of 49.4 percent. Only articles published from 1979 onward were included in order to better represent modern technique. This was 42 papers, of which those with poor outcomes were excluded. The 12 papers used intentionally were biased in favor of arthrodesis. The papers used were diverse and had populations best reflecting the study's control group. Chairman Kirkpatrick pointed out that the literature review may have been more of a systematic review than a meta-analysis.

Dr. Mann addressed Dr. Pfeffer's question about subtalar joint analysis. The subtalar joint is often affected in patients with rheumatoid arthritis. In the study, no patients had progression in subtalar joint problems or became symptomatic. Dr. Saltzman's articles showed that fusion can cause arthritis of the subtalar joint.

Dr. Mann addressed osteophytes. At 11 months, there were 8 osteophystes in 158 patients. After cleanup and debridement, those patients with osteophytes did well. They could walk immediately after the corrective surgery. Total recovery was 2 to 3 weeks.

Dr. Saltzman discussed radiographic failures, which were loosening or migrating implants. There was no criteria, but 4 mm or more of settling was chosen as an arbitrary cut-off point. It was later discovered that some patients marked as radiographic failures were not failures and that settling or migration was not progressing. There were five patients who migrated in the first six months then stopped. Those patients had the same radiographic results at 12 months, 24 months, and 48 months. Success was confirmed by the clinical endpoints, so the patients were reclassified. He noted that the x-rays were subject to misreading due to rotation of the leg, and some patients appeared to be migrating in early radiographs and turned out to not be in later radiographs. He stressed that 48 month data was not used to back-form 24 month data.

Paul Postak, a Link consultant from the laboratory where the pre-clinical testing occurred, addressed device packaging. The storage limit is five years, and the packaging is industry standard. Dr. Mayor said there was research demonstrating that the industry standard was insufficient. Mr. Postak said retrieval analysis was not part of the protocol, though he had studied similar packaging with other devices and found it effective. However, the data was not for this device, and there is no protocol to test oxidation levels and mechanical properties in retrievals of this device. Chairman Kirkpatrick said that the Sponsor should be aware of and complying with ASTM standards.

Dr. Coughlin said there were four deaths in the study, none related to the implant. He further said that the FDA approved of the safety delta at the beginning of the study. Although a smaller delta would have been better, it would have required a larger sample

and longer study. Satisfaction scores were similar for STAR and arthrodesis patients, but that may be a function of control patients not knowing the potential benefit of the STAR device. He noted that pain relief was the same for both groups. The clinical difference is that STAR patients can walk up a slope, and fusion patients cannot. The function of the patient tells the true story.

Dr. Pfeffer asked whether BMI or weight were the more appropriate exclusion criterion. Dr. Coughlin said weight is the more appropriate measure, since it addresses the limit of the device.

Dr. Coughlin agreed that subtalar motion should have been measured but estimated that not measuring it based the STAR population more than the control. He offered clarification on the on the PAS. The plan was to get standing x-rays, AP lateral of the ankle of all patients pre-op and years one, two, four, and eight. Those intervals should show any migration.

Dr. Pfeffer asked for clarification on patients who had less than 14 degrees of motion on hind foot, which was higher in the control (53 percent) than in the STAR group (27 percent). The distribution does not favor STAR, but it predicts poor results in the fusion group. Dr. Mann responded that it was true but that the patients had enough movement to get around. Patients with a joint deteriorated prior to surgery would have been excluded. Dr. Saltzman pointed out that measurement of motion around the ankle is difficult and that the measurement was of total ankle movement, which would be stiff. Dr. Pfeffer pointed out that the Saltzman criteria used in Dr. Pyevich's agility study would have been a better measure. Dr. Coughlin agreed that radiographic range of motion studies were not performed due to the amount of x-raying involved.

Dr. Jeanette Ahrens said there was a mistake in FDA slide 39 and that the Sponsor met the overall success rate with both pivotal and CA studies. She addressed the CA safety success rate. The imputations on the radiographic data and the various analyses demonstrated non-inferiority with the control compared to CA. An interim analysis was implied, but it was not an interim analysis, due to three missing patients. Propensity-adjusted and covariate adjusted analyses did not change the conclusions from the unadjusted analysis. They could not adjust entirely for the differences. Dr. Popovic said that the proper time to make corrections had passed.

Chairman Kirkpatrick suggested to the Sponsor that a PE within three months of a surgery is procedure-related, though perhaps not implant-related. It is reportable.

Dr. Propert asked whether or not the radiographs got the same review in the control and STAR groups. Dr. Coughlin said that the control radiographs were not independently reviewed.

Dr. Pfeffer asked the Sponsor about tibial trials. Mr. Greenberg said none are planned, since the results in Dr. Anderson's paper were not impressive.

PANEL QUESTIONS

1) The applicant has revised the pivotal radiographic analysis that was initially provided in the PMA. This revised analysis impacts a total of 12 STAR patients.

(a) seven (7) patients who did not meet the original analysis definition of success at 6 or 12 months and who were radiographic successes at 24 months, but were carried forward as radiographic failures, and

(b) five (5) patients who were radiographic failures, but who were considered clinical successes.

Under the original PMA protocol, the 15% non-inferiority margin delta for safety was not met. The delta is met by including these 12 patients as safety successes. Please comment on the appropriateness of the revised analyses and the impact of these changes on the interpretation of the patient safety and overall safety success rates for the study.

The Panel's consensus was that, from a purist point of view, the change was inappropriate, but it was a realistic way to look at the data. The Panel did not know whether or not radiographic failures correlated to clinical failures. Mr. Melkerson asked for further clarification on how the differences between radiographic and clinical success would affect labeling. Chairman Kirkpatrick suggested that the two issues, radiographic success and clinical success, be presented separately.

2) Fractures of the mobile bearing have been noted in the applicant's informal retrieval analysis. Fractures have also been reported in literature. Functional wear testing performed by the applicant has not replicated this clinical failure mode. The compressive load used during testing is less half of what the Agency considers worst case.

Though fracture rates are relatively low, please comment on the adequacy of the functional wear testing and please discuss whether any additional pre-clinical testing would be helpful to address long-term device durability.

The Panel had concerns about additional preclinical testing that could be considered from two standpoints. One was the long-term durability or wear. The other was that fracture may be related to long term wear or to other aspects such as acute trauma or fatigue; the cause is unclear. Further investigation to replicate the mechanism may be beneficial, but specific methods of determining durability are under debate. Finite element modeling is a quick way of doing it, but there are concerns about the long-term effects of oxidation on the mechanical properties of polyethylene.

3) This continued access (CA) study consisted of 424 patients. At the time of PMA submission, the applicant indicated that 320 patients were expected for 24 month follow-up. Information was collected on 211 subjects (66%, 211/320). The applicant conducted the first CA cohort (150). 120 patients had a 24 month visit included in the database. 85 patients had radiographs digitized and available for analysis. 80 radiographs were ultimately reviewed.

Please discuss whether the data available from the CA cohort are adequate to determine if the safety success rate is comparable to the control group.

The Panel was not enthusiastic about this, but they found it acceptable. The pivotal data was good enough that the continued access would only have changed if it had come up with significant red flags of safety.

4) The applicant compared the surgical complications of the pivotal patients to the first 15 patients of the continued access (CA) to the remaining patients from the CA study. In

addition, the applicant looked at 3 investigators who only participated in the continued access study and concluded that a 15 patient learning curve was apparent.

Please comment on the adequacy of the proposed training program to ensure the sufficient surgeon preparation and knowledge of the surgical procedure.

The Panel generally agreed that the training program would be adequate and acceptable. There was a reminder that the hospital, not the FDA would be responsible for credentialing. A surgeon performing this procedure infrequently was of concern to the Panel. Panel members suggested a hotline or a website with direct dialogue for gaining information on patients and potential pitfalls.

5) The applicant has made and proposed numerous modifications to both the surgical technique and instrumentation during the course of the studies. The applicant has indicated that these modifications are adequate and have contributed to a decrease in the adverse events associated with implantation of the STAR Ankle from the pivotal study to the continued access.

Please discuss the adequacy of the Surgical Technique and Instruments (Tabs 8 & 9) available for insertion of the STAR Ankle.

The Panel consensus was that the training manual was adequate and that the training program would be sufficient. They expect that technique and instruments to evolve.

6) Under CFR 860.7(d)(1), safety is defined as reasonable assurance, based on valid scientific evidence, that the probable benefits to health under conditions of intended use, when accompanied by adequate directions for use and warnings against unsafe use, outweigh any probable risks. Considering the additional risks of surgical complications for the subject device, please discuss whether the clinical data in the PMA provide reasonable assurance that the device is safe.

The Panel was split on this question, more members saying it is safe. However, several members indicated that the safety data reflected safety in the confines of the study and expressed concerns about long term durability, five or ten years out. There were concerns about the wordings of specific phrases and indications, particularly about plantargrade foot being an essential component of a successful outcome. There were some concerns about biases inherent to the design and the uncertainty of the statistical outcomes, leading to concern about safety.

7) Under CFR 860.7(e)(1), effectiveness is defined as reasonable assurance that, in a significant portion of the population, the use of the device for its intended uses and conditions of use, when accompanied by adequate directions for use and warnings against unsafe use, will provide clinically-significant results. Considering the study outcomes, please discuss whether the clinical data in the PMA provide reasonable assurance that the device is effective.

The Panel consensus was that there was a reasonable assurance of effectiveness. Members made comparisons to other ankles, and it is at least as effective as other ankles in historical controls. There were concerns about intended uses and warnings.

8) Within Tab 13 of the Panel Pack, the applicant has proposed to conduct a two-component post-approval study (PAS), which includes:

A long-term (8-year) follow-up component with a rate of device revision or removal as the primary outcome, and

A short-term (12 month) physician learning curve component with a rate of measured complications as the primary outcome.

Please comment on the follow post-approval study issues.

a. Radiographic evaluation:

1. The adequacy of intervals and frequency of radiographic assessment;
2. The necessity for mandatory radiographic measurements;
3. The necessity for radiographic measurements on all patients to be performed by independent radiologists; and
4. The relevant radiographic parameters to measure.

b. Comparing STAR Ankle Arthroplasty to a control (e.g. arthrodesis or another type of arthroplasty) and the specific long term outcomes to be compared.

c. Addressing the long-term outcome of STAR Ankle patients who experience revision or convert to arthrodesis after STAR Ankle failure, including those STAR Ankle patients who failed in the CAS.

d. The appropriate length of follow up (8 years currently proposed).

e. Measures to minimize loss to follow-up and compensatory measures taken when it occurs.

f. The sufficiency of the proposed learning curve investigation (5 new surgeons, 125 patients, 12 month follow up) and the selection of new investigators.

The Panel addressed the separate bullet points separately. Members expressed concern about the Panel evaluating a PAS at this point in the proceeding, with the process for those discussions perhaps not in place. Due to new procedures and since a PAS was likely, the Panel moved forward with the question. For a., the radiographic evaluation, There was near-unanimous agreement that radiographs would be appropriate in follow-up. There was concern about who interpreted the radiographs. The Panel wanted to see an independent interpreter who was familiar with the device. It was also suggested that if radiolucencies develop they could be evaluated by CT scan or other relevant axial imaging study.

For item b, the Panel consensus was that a control group was not necessary. Some members felt strongly that a control was needed but would accept historical or comparative controls from the literature.

For item c, the Panel consensus was that the group of patients should be analyzed and followed, and answers should be gained from that data. Retrievals should be analyzed for lessons learned.

For item d, the Panel agreed that 8 to 10 years would be an appropriate follow-up. There were concerns about the feasibility of the follow-up and relevance to future models of the device.

For item e, the Panel agreed that it should be done, but no one knew how it would be done.

For item f, the Panel appreciated the idea of trying to study the learning curve but doubted the realism. There are no good methods for analyzing learning curves. Though the Sponsor may design a way of doing it, the information may not be valuable.

OPEN PUBLIC HEARING

Dr. Gill returned to the podium. He had presented and disclosed his conflicts in the first public hearing session. He pointed out that clinical studies have problems and that corrections are often made in the field. He mentioned some orthopaedic failures that have led to lessons that have led to clinical use. He noted that Class II versions of a similar ankle are being installed.

Rachel McGuckian from the Orthopedic Surgical Manufacturers Association (OSMA) gave a background of her organization and urged the Panel to focus on the safety and effectiveness data of the proposed device and to balance the obligation to foster safety with the obligation to foster innovation. She asked reminded the Panel of the regulatory burden and asked for careful consideration.

FDA AND SPONSOR SUMMATIONS

The FDA had no further comment. For the Sponsor, **Dr. Clanton** said that ankle arthritis surgeries go back 124 years and that the Sponsor is trying to continue the evolution of care and reduce suffering. The current standard reduces pain but eliminates motion in the ankle. Some ankles fuse improperly or become infected, and there are stress transfer effects on the adjacent joints, causing osteoarthritis changes and requiring further surgeries. Design advances have improved ankle arthoplasty results, and the study, the most detailed and the only prospective study of ankle arthoplasty and arthodesis, demonstrates superiority to fusion. European literature shows durability, over 90 percent 10-year survivorship. Major complications are low, and if the device fails, the ankle is treated with an arthrodesis, the standard of care, effectively and efficiently.

Mr. Greenberg added that this is a low-volume procedure, and the Sponsor is interested in seeing the best outcomes. He agreed that surgeons should have access to patient information and to surgical mentors. He said the manual would be updated.

PANEL DELIBERATION AND VOTE

Ms. Whittington encouraged patient education and discouraged misleading advertising. She encouraged transparency in advertising and education. Ms. Adams had no comment.

Executive Secretary Jean read the Panel recommendation options, and Chairman Kirkpatrick opened the floor. **Dr. Wright moved that the Panel recommend that device as approvable with conditions. Dr. Pfeffer seconded the motion.**

Dr. Goodman moved that the first condition be a post-approval study consistent with the Panel's discussion. Dr. Wright seconded the motion. Mr. Melkerson asked that Dr. Goodman list the questions to be addressed by the PAS. Dr. Goodman said that the PAS would address the clinical and radiographic parameters outlined by the investigators. The clinical parameters would include the BP rating system and others that the investigators feel appropriate, including AFAS ranking systems. Radiographic parameters were outlined and would include standing x-rays of the feet with specific radiographic parameters as agreed upon by investigators and the FDA to reflect the radiographic performance of the prosthesis. **Dr. Wright accepted the clarification.** Chairman Kirkpatrick suggested that the PAS would demonstrate safety by evaluating device failure as time proceeds compared to historical controls and ankle fusions in the literature. The PAS would study long-term safety issues, like polyethylene failure. Effectiveness would also be evaluated, when relevant and when failures or safety issues occurred. **The amendment was accepted by Drs. Goodman and Wright.** Mr. Melkerson commented that the burdens of safety and efficiency must be met by PMA data. Chairman Kirkpatrick clarified that the 24 month study was adequate for approval but that there were concerns about long-term safety. As safety concerns arise, efficacy can also be looked at. Ms. Adams noted that the independent review of radiographic data would be a burden. Chairman Kirkpatrick said the Sponsor and FDA would work it out, but it is part of the recommendation. Dr. Skinner offered an amendment to remove the recommendation of independent radiological review. Dr. Goodman did not accept the amendment. **The first condition carried 4 to 1 with Dr. Mayor abstaining.**

Dr. Pfeffer moved a second condition, an upper weight restriction to be placed on the implant, supported by post-approval biomechanical wear studies to be completed within a reasonable time frame. **Dr. Goodman seconded the motion. Dr. Skinner offered an amendment**, that the weight restriction be reevaluated after the wear studies, rather than changed. **Drs. Pfeffer and Goodman accepted the amendment.** Dr. Wright expressed concern about omitting the obese from the study and taking the decision out of the surgeons' hands. Chairman Kirkpatrick said the PAS should wear at 6,000 N to determine whether or not a 250 lb. patient would be subject to early failure or major problems. **The motion carried 5 to 0 with Dr. Mayor abstaining.**

Dr. Goodman moved a condition that the surgical manual be updated. **Chairman Kirkpatrick seconded the** motion and commented that the surgical techniques had changed since the manual was written. **The motion carried 5-0 with Dr. Mayor abstaining.**

Dr. Pfeffer moved that the education of the surgeons be formalized and that the information on appropriate patient selection be put in a specific, surgeon-directed, education document. Ms. Whittington agreed, pointing out that having the selection criteria on hand would make it easier for a surgeon whose patient demands a device to demonstrate contraindication. Both the patient and physician materials should have the

selection criteria. Chairman Kirkpatrick pointed out that the information would be updated in the surgical technique brochure. Ms. Adams pointed out that it would be in the training as well. **Dr. Pfeffer withdrew the condition.**

Dr. Pfeffer moved the condition that understandable (6th grade level) patient education material reflecting the warnings on the package insert, especially addressing outcomes, risks, and benefits, be made available to patients. **Dr. Skinner seconded** the motion and proposed that the data be on the Link website. **Dr. Pfeffer accepted the amendment. The motion carried 5-0 with Dr. Mayor abstaining.**

Chairman Kirkpatrick moved that deformity be removed from the indications, since it is one of the contraindications. **Dr. Pfeffer seconded the motion** and commented that the Sponsor should straighten out the contradictions**. Dr. Mayor offered a friendly amendment** to include the elimination of "primary arthrosis" for "degenerative arthrosis" in the indications, which **the mover and seconder accepted**. **The motion carried 4 to 0, with Drs. Mayor and Propert abstaining.**

Chairman Kirkpatrick called for other conditions. Hearing none, he called for a vote on the primary motion. **The motion carried, 4 to 2.**

Dr. Mayor said he voted against the motion because of long term failures and subtalar problems. He was disappointed with the Sponsor's assessment of polyethylene. His abstentions on the conditions reflected his intention to vote against approving the device. He made some recommendations for the FDA to consider. He noted that the extra small tibial implant is not the same shape as the other implants. He suggested removing a phrase from the warnings and precautions indicating that apparently-undamaged implants may have small defects and internal stress patterns leading to premature failure. He noted another warning that said not to use components if the package is opened, but the package must be opened before the device can be implanted. He suggested that the surgical technique guide's illustrations show the ankle in a more meaningful position. He said, in his experience, the differences in patient mobility between arthroplasty and arthrodesis are exaggerated. He ended by saying that the draft proposal for the PAS should replace the term, "conservative therapy" with "non-operative therapy." **Dr. Pfeffer** felt the mandated wear studies and the broad knowledge of the implant will mitigate the concerns. **Dr. Propert** said it was a difficult decision. She saw reasonable assurance of effectiveness, but not valid scientific evidence of safety. **Dr. Skinner** felt that safety, efficacy, and noninferiority were demonstrated. **Dr. Goodman** commented that the rigidity of the process excluded some of Dr. Mayor's objections, which could have become conditions. **Chairman Kirkpatrick** said that Dr. Mayor's recommendations would be incorporated in the FDA's actions. **Dr. Goodman** said data are never perfect and long term safety remains unknown, so he encouraged the sponsor to follow the patients closely and notify the FDA if things go wrong. **Dr. Wright** said he came close to voting the other way and that the study design was his largest complaint, that arthrodesis and joint replacements are two different things and the implant should have been compared to another implant. However, this implant is not worse than anything else on the market, though he is not convinced it is any better. **Ms. Whittington** also had concerns about outcome data and the comparative body. **Ms. Adams** said the Sponsor did a good but imperfect job. She acknowledged the work of the FDA and the Chairman. **Chairman Kirkpatrick** thanked the Sponsor, FDA, Panel, and all participants. **He adjourned the meeting at 4:33 p.m.**

I certify that I attended this meeting of the Orthopaedic and Rehabilitation Devices Panel on April 24, 2007, and that these minutes accurately reflect what transpired.

Ronald P. Jean, PhD
Executive Secretary

I approve the minutes of this meeting as recorded in this summary.

John S. Kirkpatrick, MD
Acting Chairman

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