

STAR Ankle IDE Summary Outcomes Data

The IDE clinical study shows the STAR Ankle to be superior with overall outcomes to fusion.¹ Continued Access patient outcomes showed even greater, and sustained, improvement compared to fusion due to surgical experience and refinements in technique.

The primary outcome measure was the Buechel-Pappas (BP) scoring system (See Attachment A). All measures were defined *a priori*. 24-month study results presented to the FDA include the following:

Primary Efficacy Endpoint: Mean BP Score²

	12 Months			24 Months		
	STAR (n=142)	Control (n=47)	<i>p</i> -value	STAR (n=142)	Control (n=47)	<i>p</i> -value
Total (SD)	80.7 (14.3)	65.9 (17.0)	<0.001	81.6 (14.0)	69.7 (18.8)	<0.001

STAR Ankle secondary efficacy outcome measures³ also showed arthroplasty to be better than arthrodesis at 24 months.

Secondary Outcome Measure: Pain VAS

Improvement From Baseline	12 Months			24 Months		
	STAR (n=144)	Control (n=51)	<i>p</i> -value	STAR (n=144)	Control (n=45)	<i>p</i> -value
Mean (SD)	51.1 (24.3)	43.5 (27.0)	0.118	51.8 (26.5)	44.6 (27.3)	0.089

¹ Orthopedic and Rehabilitation Devices Advisory Panel Meeting, April 24, 2007: Link Orthopaedics Scandinavian Total Ankle Replacement System (S.T.A.R. Ankle) PMA – P050050
(Source: <http://www.fda.gov/ohrms/dockets/AC/07/slides/2007-4299s1-02.pdf>) (accessed 4/23/2009)

² A patient's Buechel-Pappas ("BP") score includes a measure of pain, function, range of motion, and deformity, on an overall composite scale of 100 points. See Appendix A.

The STAR Ankle was proven to be as safe as fusion at 12 months and 24 months of rigorous study. In its Summary of Safety & Effectiveness, the FDA concluded:

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

Long-term use within and outside the United States further support's the FDA's conclusion, that STAR Ankle is safe, effective and durable in properly selected patients when implanted by experienced surgeons.

Overall Safety Profile

	<u>12 Months</u>				<u>24 Months</u>			
	<u>STAR</u>		<u>Control</u>		<u>STAR</u>		<u>Control</u>	
	n/N	%	n/N	%	n/N	%	n/N	%
Safety Success	100/136	80.1	50/57	87.7	101/142	71.1	43/52	82.7
No Revisions or Removals	125/136	91.9	54/57	94.7	122/142	81.0	47/52	90.4
No Major Complications	126/136	92.6	56/57	98.2	128/142	90.1	51/52	98.1
Radiographic Success	120/131	91.6	51/57	89.5	117/138	84.8	46/52	88.5

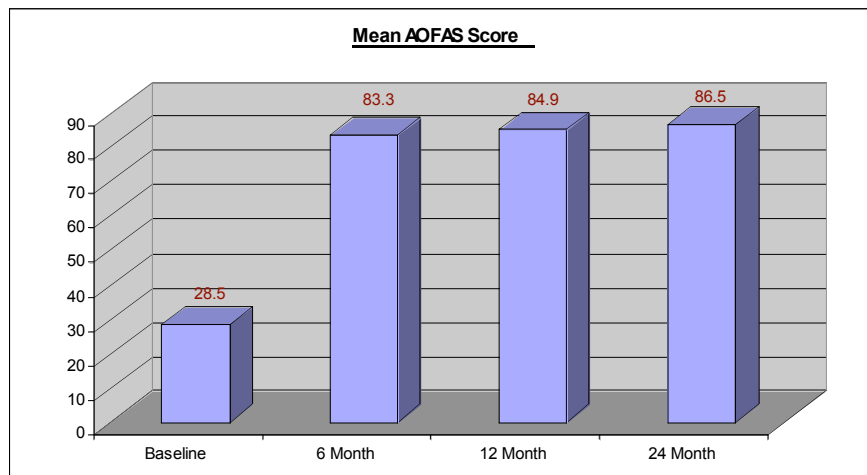
Micro-outcomes related to the Buechel-Pappas results from the STAR Ankle IDE study included real-world criteria such as climbing stairs, standing, supporting one's self upright, and walking. The STAR Ankle equaled or exceeded fusion in all efficacy categories studied.

**BP Subscale Comparison:
S.T.A.R. Ankle versus Arthrodesis at 24 Months**

BP Subscale	STAR Ankle (N=143)	Control (N=48)	P – value
Deformity	1.9 (113)	0.4 (1.2)	< 0.001
Function	13.4(7.3)	9.7 (8.7)	0.004
Stairs	1.6 (2.1)	0.9 (2)	0.039
Standing	3.4 (2.8)	1.7 (3.3)	< 0.001
Support	1.7 (2.2)	0.8 (1.9)	0.016
Walking	2.6 (1.9)	2.7 (1.9)	0.746
Limp	4.1 (2.2)	3.4 (3.4)	0.114
Pain	21.5 (9.6)	19.2 (9.4)	0.14
ROM	3.6 (3.7)	- 3.7 (5.1)	< 0.001
TOTAL	40.5 (15.1)	26.3 (17.1)	< 0.001

As reported above, arthroplasty is better than, or superior to, arthrodesis over a 24-month period of time. The efficacy data above indicate favorable results for the STAR Ankle, as it boasted a change in BP score of 40.5 points 24 months after surgery, compared to the 26.3-point change among the fusion control group ($p < 0.001$). The outcomes are attributable to the device. Moreover, considerably more S.T.A.R. Ankle patients had an improvement in BP score of greater than or equal to 40 points compared to the control. The mean BP and VAS scores for STAR Ankle patients at 24 months also proved the device’s non-inferiority to the fusion control patients in terms of device effectiveness.

Patient improvement with STAR also was measured using the AOFAS scoring system. The mean AOFAS scores shown below demonstrate significant and sustained outcomes. Additionally, the results confirm similar patient outcomes to patient improvements in BP discussed previously.



Finally, the STAR IDE demonstrated similar perioperative outcomes for the treatment and control groups. Operating room and anesthesia time were nearly identical. Average length of stay (LOS) (approximately 3 days) is comparable between STAR and fusion.

Comparable Perioperative Outcomes – S.T.A.R. IDE Study

	STAR (N=158)	Control (N=66)	p-value
OR Time (Hours)	2.2 (0.5)	2.4 (1.2)	0.613
Anesthesia Time (Hours)	3.1 (0.7)	3.2 (1.3)	0.783
Estimated Blood Loss	53.1 (44.5)	75.3 (89.9)	0.318

Continued Access Outcomes

The FDA has traditionally permitted sponsors of clinical investigations to continue to enroll subjects at a pre-determined rate while a marketing application is being prepared by the sponsor or reviewed by the Office of Device Evaluation if there is preliminary evidence that the device is likely to be effective, and no significant safety concerns have been identified for the proposed indication. The STAR Ankle’s Continued Access (“CA”) Study allowed researchers to collect additional safety and effectiveness data in a cohort of 352 patients.

Pivotal v. Continued Access (CA) Success Rates: 24 Month Results

Success	Fusion Patients	Pivotal STAR Patients	CA STAR Patients	Difference (CA STAR-Fusion)
Patient success*	7/51 (13.7%)	70/142 (49.3%)	172/276 (62.3%)	48.6%
Efficacy success	7/47 (14.9%)	83/142 (58.5%)	239/314 (76.1%)	61.2%
Safety success	43/52 (82.7%)	113/142 (79.6%)	233/273 (85.3%)	2.7%

*Based on both clinical and radiographic safety success criteria.

Outcomes from the STAR Continued Access study arm demonstrate not only enhanced safety and efficacy when compared to fusion, but also improved function and pain relief beyond already impressive results in the pivotal trial.

BP Subscale Comparison:
STAR Ankle, Arthrodesis, and Continued Access at 24 Months

Subscale	STAR Ankle (N=143)	Control (N=48)	P – value	Continued Access (N=314)
Deformity	1.9 (1.13)	0.4 (1.2)	< 0.001	0.9 (1.2)
Function	13.4(7.3)	9.7 (8.7)	0.004	17.9 (7.2)
Stairs	1.6 (2.1)	0.9 (2)	0.039	2.5 (2.2)
Standing	3.4 (2.8)	1.7 (3.3)	< 0.001	4.2 (2.6)
Support	1.7 (2.2)	0.8 (1.9)	0.016	2.3 (2.4)
Walking	2.6 (1.9)	2.7 (1.9)	0.746	3.7 (2.0)
Limp	4.1 (2.2)	3.4 (3.4)	0.114	5.2 (1.9)
Pain	21.5 (9.6)	19.2 (9.4)	0.14	24.2 (7.5)
ROM	3.6 (3.7)	- 3.7 (5.1)	< 0.001	3.7 (3.5)
TOTAL	40.5 (15.1)	26.3 (17.1)	< 0.001	46.7 (13.0)

With any surgical procedure, clinical outcomes often improve based upon number of cases performed. Numerous clinical articles have addressed this issue of volume-based outcomes.^{4,5}

Long-Term Case Series Data

Long-term outcomes demonstrate STAR ankle safety, effectiveness, and long-term durability. Duke University Medical Center researchers maintain a long-term registry of patients receiving ankle arthroplasty⁶. Within this registry, 91 STAR ankle implants (88 patients) have reportable data for pain, function, and quality of life (SF-36). Nearly half of all cases relate to post-traumatic arthritis, 34 percent were diagnosed with osteoarthritis of the ankle, and 9 percent were diagnosed with rheumatoid arthritis. Average age was

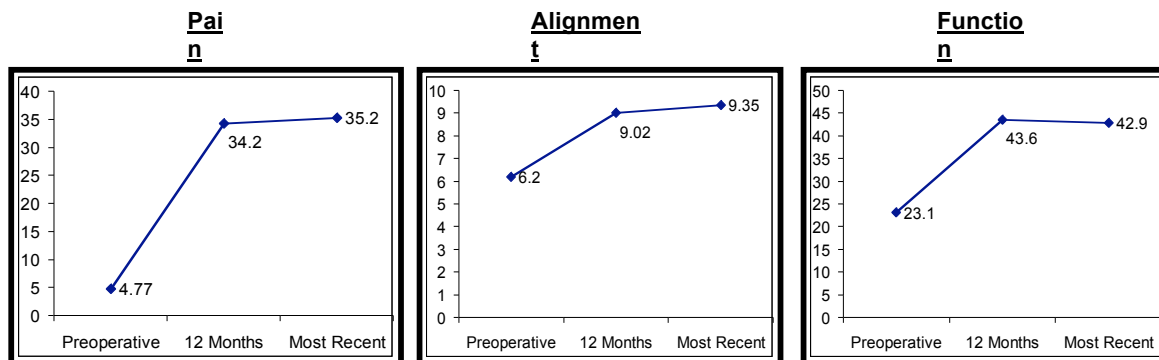
⁴ Jain, N et al. The Relationship Between Surgeon and Hospital Volume and Outcomes for Shoulder Arthroplasty. *JBJS*, Vol 86, pp 496-505 (2004). Patients who have a total shoulder arthroplasty or hemiarthroplasty performed by a high-volume surgeon or in a high-volume hospital are more likely to have a better outcome.

⁵ Hervey, SL et al. Provider Volume of Total Knee Arthroplasties and Patient Outcomes in the HCUP-Nationwide Inpatient Sample. *JBJS*, Vol 85-A, No 9, pp 1775-83 (2003) Patients treated by providers with lower caseload volumes had higher rates of mortality following total knee arthroplasty.

⁶ Pre-publication data. Source: DeOrio, M, Midterm Follow-Up of STAR Prosthesis Implanted by a Single Surgeon, AOFAS Summer Meeting (Presentation) (June 26, 2008); Nunley et al, Pre-Publication Analysis of Long-Term Outcomes from Duke University Registry of Total Ankle Arthroplasty Patients.

64 years, median weight was 183 pounds (28.2 BMI), and median duration since implant was 5.8 years (1998-2007).

The VAS score pain reduction went from approximately 72 to approximately 8.0 ($p < 0.002$). Overall physical health in the study cohort went from a pre-operative score of 36.9 to 74.3 for the most recent measured cohort outcomes. STAR Ankle patients demonstrated significant and sustained improvement in AOFAS hindfoot scores in pain, alignment, and function.



Researchers at Oakland Bone & Joint also maintain a long-term registry of patients receiving ankle arthroplasty. Within this registry, they have identified 84 STAR cases (80 total patients) with reportable data for pain, function, motion, and adjacent joint arthritis.⁷ Average time to follow-up is 8.7 years. Key findings include the following:

- Five year survival for the STAR is 98.6% with 87.5% survival at 10 years.
- Range of motion increased approximately 6 degrees from 32.1 degrees to 38.3 degrees.
- AOFAS scores increased from 42 to 77 points.
- Pain improved from 7.2 to 32.4 on a 40-point scale while functional improvement increased from 26.4 to 41.5 on a 50-point scale.
- 80% of patients had no progression of arthritis at either the subtalar or talonavicular joints.
- 92% Patient Satisfaction

Arthrodesis

Ankle arthrodesis has been the standard of care for some time. While the literature supports the use of arthrodesis, advancements in the technology and technique for ankle arthroplasty supports its use in well selected patients by qualified physicians.

⁷ Mann, RA et al, Scandinavian Total Ankle Replacement (STAR): Five to Ten Year Results Pre-Publication (Sept 2008)

Arthrodesis is meant to relieve pain and provide stability for the ankle. However, it is well known that the procedure includes a long period of convalescence and immobilization of the ankle (generally 12-20 weeks).^{8,9} Complications related to arthrodesis are common, including delayed bone healing, malunion, nonunion, pseudoarthritis, increased stress on the smaller joints of the foot, loss of motion in the subtalar joint, and accelerated arthritis in the ipsilateral foot. Arthrodesis also is known to cause breakdown of the midfoot joint. Finally, arthrodesis can lead to a reduction in activities of daily living such as walking on uneven surfaces, running, climbing stairs, and getting out of a chair.

Complications associated with total ankle replacement have included malleolar fracture, fibular and talar fracture, damage to neurovascular structures, infections, valgus impingement, delayed wound healing, and skin necrosis.¹⁰ Overcoming complications, we at St. Alphonsus routinely evaluate individual cases performed to identify any further opportunities for improvement. We have been able to limit complications at our center through rigorous patient selection and refinement of our own skills. Overall, improvements in surgical technique and instrumentation likely contribute to the lower incidence of major complications in the Continued Access arm of the STAR study.

STAR Ankle Complications – Pivotal Trial v. Continued Access

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

Finally, the goal of total ankle replacement is to reduce pain and restore as much function as possible. As is the case with total hip and knee replacements, patients undergoing total ankle replacement will not return to a normal range of motion. Instead, incremental increases in range of motion are the expected outcome.

⁸ Ferkel, RD, Hewitt M. Long-term results of arthroscopic ankle arthrodesis. *Foot Ankle Int* 2005; 26-4:275-80.

⁹ Haddad SL, Coetzee JC, Estok R, Fahrback K, Banel D, Nalysnyk L. Intermediate and long-term outcomes of total ankle arthroplasty and ankle arthrodesis. A systematic review of the literature. *J Bone Joint Surg Am* 2007; 89-9:1899-905.

¹⁰ Conti, SF et al. Complications of total ankle replacement. *Clin Orthop Relat Res*, Vol 391, pp 105-114 (2001)

Patient Selection Criteria Are Important to Total Ankle Replacement Treatment Success

Patient selection remains a key element in achieving successful ankle arthroplasty. It is important to identify patients with characteristics that trend well with overall success. Conversely, it is equally important to identify patients who would not be good candidates for this procedure. Following the STAR Ankle criteria for patient selection is recommended. Inclusion / exclusion criteria include the following:

Inclusion criteria:

- Moderate or severe pain, loss of mobility, and function of the ankle (BP total score less than 50 and BP pain score \leq 20)
- Primary arthritis, post-traumatic arthritis, or rheumatoid arthritis
- At least six months of conservative care treatment for severe ankle conditions, confirmed by patient medical history, radiograph studies, and medication record.

- Patients who have not reached skeletal maturity
- Active or prior deep infection in the ankle joint or adjacent bones
- Prior arthrodesis at the involved site
- History of prior mental illness or demonstration that mental capacity may interfere with treatment
- Obesity defined as patients weighing greater than 250 pounds
- History of current or prior drug use or alcoholism
- Any physical condition precluding major surgery
- Hindfoot malpositioned by more than 35 degrees or forefoot malalignment that would preclude a plantigrade foot
- Lower extremity vascular insufficiency demonstrated by Doppler arterial pressure
- Avascular necrosis of the talus
- Inadequate skin coverage about the ankle joint
- Severe deformity that would not normally be eligible for surgery
- Prior surgery and/or injury that has adversely affected the ankle bone stock
- Severe osteoporotic or osteopenic condition that may lead to inadequate implant fixation
- Insufficient ligament support
- Motor dysfunction due to neuromuscular impairment

Biomechanical Differences

The study of ankle arthroplasty devices over a 30+ year period has allowed investigators to address mechanisms critical to patient success. As noted within the literature, early versions of ankle arthroplasty devices showed inferior results to arthrodesis. Significant improvements in technology design have resulted in superior technologies, particularly over the past decade.^{11,12,13} Specifically, three-part, uncemented mobile-bearing implants allow the patient a greater mobility on its axes of rotation, as the most successful prosthetic designs have mimicked the normal kinematics and kinetics of the ankle joint.¹³ This motion is intended to reduce the incidence of adjacent joint arthritis, presenting direct advantages over arthrodesis and earlier-generation arthroplasty devices.

Radiolucency evaluations conducted on the Agility™ and other total ankle replacement devices has shown a potential for ballooning lysis, and may be indicative of device migration issues.^{14,15,16,17} However, such issues are confined to the particular devices on which the previous studies are based, as was the case with Pyevich's 1998 study of the Agility™, and do not extend to an evaluation of the STAR Ankle. Kofoed, et al's findings of radiographic loosening in STAR Ankle patients who were either uncemented (4%) or cemented (17%) speaks to the success seen with the STAR Ankle's uncemented design characteristics, as well as its long-term efficacy in this 12-year study.¹⁸

An independent radiographic assessment of STAR Ankle patients at 24 months was presented at the April 2007 FDA panel meeting. Efficacy success was found to be maintained at 84.3%, and safety success at 88.9%. Success criteria included no device fracture or migration.

¹¹ Buechel, FF et al. Survivorship and clinical evaluation of cementless, meniscal-bearing total ankle replacements. *Foot Ankle*, Vol 8, pp 279-90 (1992)

¹² Kofoed, H et al. Ankle arthroplasty for rheumatoid arthritis and osteoarthritis: prospective long-term study of cemented replacements. *JBJs*, Vol 80, pp 328-332 (1998)

¹³ Hintermann, B. Total Ankle Arthroplasty: Historical Overview, Current Concepts and Future Perspectives. Springer-Verlag/Wien, New York, NY (2005) (ref Gill, LH. Principles of joint arthroplasty as applied to the ankle. AAOS Instruct. Course Lect., Vol 51, pp 117-28 (2002)

¹⁴ Pyevich, MT et al. Total Ankle Arthroplasty: a Unique Design. *JBJs*, Vol 80-A, No 10, pp 1410-20 (1998)

¹⁵ Rippstein, PF. Clinical experiences with three different designs of ankle prostheses. *Foot Ankle Clin*, Vol 7, No 4, pp 817-831 (2002)

¹⁶ Coetzee, JC et al. Accurate Measurement of Ankle Range of Motion after Total Ankle Arthroplasty. *Clin Orthop Relat Res*, No 424, pp 27-31 (2004)

¹⁷ Knecht, SI et al. The Agility Total Ankle Arthroplasty: Seven to Sixteen-Year Follow-Up. *JBJs*, Vol 86-A, No 6, pp 1161-71 (2004)

¹⁸ Kofoed, H et al. Scandinavian Total Ankle Replacement (STAR). *Clin Orthop Relat Res*, No 424, pp 73-79 (2004)

Revisions and Removals

All surgical procedures include the limited risk of complications related to device-related events, patient adherence to recovery guidelines, or the surgical procedure. Total ankle replacement devices are no different. What is important, particularly for total ankle replacement, is that revisions and replacements can be performed safely and effectively. Improvements in device design and surgical procedure are reducing the rate of occurrence. Further, newer devices like the STAR, with limited bone resection, offer the opportunity to revise or replace a total ankle replacement device with another device or ankle fusion. While amputation remains a potential negative outcome related to total ankle replacement, it is important to note that amputations also are a negative outcome related to ankle fusion and appear to occur with similar frequency.¹⁹ No amputations were reported in the STAR IDE pivotal study; one amputation (out of 352 cases) was reported in the Continued Access study.

Despite the usual risk of complications following surgery, a clear advantage of total ankle replacement over fusion is the ability of a surgeon to remove an arthroplasty device, and subsequently fuse the ankle or perform other surgical procedures. The STAR Ankle pivotal IDE study saw a higher rate of early major revision surgeries in STAR Ankle patients than in fusion patients. This result would be consistent with studies of early revisions by Soohoo, et al and Haddad, et al.^{20,21} However, the rates of major revision surgeries at 24 months post-operative were far more similar to the fusion and STAR Ankle Continued Access study patients. The continued access subgroup required half as many secondary minor and major surgeries as did the pivotal subgroup.

¹⁹ Haddad, SL et al. Intermediate and long-term outcomes of total ankle arthroplasty and ankle arthrodesis. A systematic review of the literature. *JBJS*, Vol 89, No 9, pp 1899-1905 (2007)

²⁰ SooHoo, NF et al. Comparison of reoperation rates following arthrodesis and total ankle arthroplasty. *JBJS*, Vol 86-A, No 6, pp 1172-8 (2004)

²¹ Haddad, SL et al. Intermediate and long-term outcomes of total ankle arthroplasty and ankle arthrodesis. A systematic review of the literature. *JBJS*, Vol 89, No 9, pp 1899-1905 (2007).