ATTUNE® Knee System Early Performance: Minimum Two Year Clinical Results

Kim Dwyer, Ph.D., CCRA[1], Richard E. Jones, MD[2], Jim Lesko, Ph.D.[3], John Leopold, M.S.[4], and Rodrigo Diaz, M.D.[5]

1) Senior Manager, Clinical Research, *DePuy Synthes Companies*, 2) Professor Orthopaedics, University of Texas Southwestern Medical Center; Consultant, Orthopedic Specialists, Dallas, TX, 3) Manager of Biostatistics, *DePuy Synthes Companies*, 4) Biostatistician, *DePuy Synthes Companies*, 5) Medical Director - Strategic Medical Affairs & Medical Sciences, *DePuy Synthes Companies*

INTRODUCTION

Each year, Total Knee Arthroplasty (TKA) relieves pain and restores function and mobility for patients with arthritis pain. Although it is widely recognized as one of the most performed and most successful surgical procedures, research shows that between 10 and 20% of TKA patients are not satisfied.[1,2,3,4] It was the goal of *DePuy Synthes Companies of Johnson & Johnson* to design a total knee system that works with the surgeon and surgical teams around the world to positively impact patient satisfaction, while improving hospital efficiency.

The ATTUNE® Knee System was designed over a 6-year period with key system goals to:

- Improve function through motion and stability
- Improve patient fit
- Improve patello-femoral function
- Improve design and materials for implant durability
- Advance surgical process for implant positioning and OR efficiency.

Following regulatory approvals, the ATTUNE Knee was introduced in a phased approach beginning in November 2011. Prospective data collection in a company joint registry was initiated at the time of initial product introduction and the purpose of this report is to review the minimum 2-year clinical data of the first knees to reach that endpoint.

MATERIALS AND METHODS

There are currently three primary sources of clinical data on the ATTUNE Knee System: 1) data from the ATTUNE Knee Early Performance Registry, 2) UK National Joint Registry Supplier Feedback and 3) data from ongoing clinical studies. The most mature source, the Early Performance Registry, will be described herein. Future sources of data may also include: 4) information from the Beyond Compliance partnership in the UK and 5) Investigator Initiated Studies.

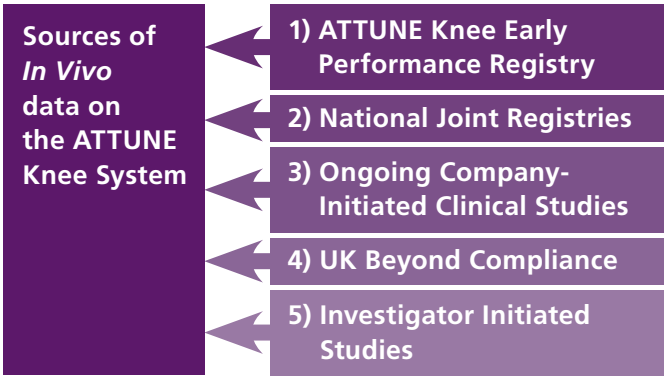


Figure 1: Sources of *In Vivo* data on the ATTUNE Knee.
The Early Performance Registry is the focus of this report.

Early Performance Registry

The ATTUNE Knee Early Performance Registry was established to assess the early post-operative clinical performance of the ATTUNE Knee and to assist *DePuy Synthes Com*panies *of Johnson & Johnson* with decisions regarding commercialization. It was planned that surgeons from among the design team would enroll 1,200 knees, consisting of 300 knees per configuration (Cruciate Retaining Fixed Bearing [CR FB], Cruciate Retaining Rotating Platform [CR RP], Posterior Stabilized Fixed Bearing [PS FB], and Posterior Stabilized Rotating Platform [PS RP]), and follow these knees to a final endpoint of 6 months post-operatively. To accommodate surgeon-to-surgeon variation, it was decided that no one surgeon should contribute more than 100 knees per configuration for the analyses in the final summary report for this registry. A protocol was developed and Institutional Review Board (IRB) approval was obtained at all clinical sites prior to enrollment.

From this initial Early Performance Registry, a subset of surgeons was identified to continue following their patients beyond 6 months, to the 2-year end point, consistent with their standard of care. All of these surgeons are fellowship trained, board certified orthopaedic surgeons with many years of experience implanting TKAs and conducting clinical research.

The data collection included clinical results using the American Knee Society (AKS) Score and all Adverse Events (AE), which included: all procedure-related adverse events, all device-related adverse events, and all serious adverse events.[A] Adverse event reporting included both systemic and operative site events.

Data on 782 ATTUNE Knees (724 patients)[5], that were implanted at 15 centers (11 US, 3 UK, 1 Germany) and which had a primary TKA at least 549 days prior to data extract (31 Jan 2014) are summarized in this report. This is referred to as the Safety Dataset. The Efficacy Dataset is comprised of the subset of patients who have had a 2-year clinic evaluation.

Table 1: *DePuy Synthes Companies* Registry: Multi-Center Site Details

Center	Number of Knees Implanted Through 31 Jan 2014	Subset of Knees Included in this Report	
		Elapsed Time ≥ 549 Days SAFETY DATASET N=782	Elapsed Time ≥ 549 Days & 2 Year Visit on File EFFICACY DATASET N=100
Site 1	408	86	14
Site 2	1	1	
Site 3	202	52	8
Site 4	127	84	
Site 5	470	161	32
Site 6	179	54	6
Site 7	58	1	
Site 8	47	13	
Site 9	55	12	
Site 10	189	27	4
Site 11	398	98	17
Site 12	91	15	5
Site 13	107	48	
Site 14	422	111	8
Site 15	86	19	6
Total	2840	782	100

[A] A Serious Adverse Event (SAE) is defined as any untoward medical occurrence that: a) results in death; b) is a life-threatening illness or injury; c) requires inpatient hospitalization or prolongation of existing hospitalization; d) results in persistent or significant disability/incapacity; e) is a congenital /birth defect; f) necessitates medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure anomaly or function; or g) other serious (Important Medical Events)-report when the event does not fit the other outcomes, but the event may jeopardize the patient and may require medical or surgical intervention (treatment) to prevent one of the other outcomes.

Demographics

The demographics of the Safety Dataset are summarized below and are considered representative of a typical primary TKA population.

For the subset of 100 patients with 2-year follow-up on file the average duration of follow-up was 673 days ± 62 days (range: 549-783 days).

Table 2: ATTUNE Knee Early Performance Safety Dataset, Subject Demographics

SUMMARY	STATISTIC OR LEVEL	ATTUNE Knees N=782 knees
Age (Years)	Mean (Standard Deviation, SD)	67.2 (8.8)
Gender	Female	477 (61%)
	Male	302 (39%)
	Missing	3 (0.3%)
Height (Inches)	Mean (Standard Deviation)	66.6 (4.7)
Weight (Pounds)	Mean (Standard Deviation)	189 (41.2)
Body Mass Index	Mean (Standard Deviation)	30.0 (7.1)
Diagnosis	Osteoarthritis	93%
	Post Traumatic Arthritis	3%
	Other	2%
	Missing Diagnosis	1%
	Rheumatoid Arthritis	1%
Configurations	508 CR knees; 274 PS knees; RP : FB mix = 107 : 675 knees	

CLINICAL RESULTS

Summaries of AKS Score, flexion, extension and the pain sub-score on the AKS in the various follow-up intervals are provided in Tables 3-6 using the Efficacy Dataset. Since pre-operative (pre-op) functional performance, especially motion, is a strong predictor of post-operative outcomes, the change from baseline (pre-op) data is also included. A positive change from baseline in AKS Score and knee flexion reflects an improved AKS score and greater range of motion, respectively. A negative change from baseline for extension reflects a reduction in flexion contractures.

- At 6 months, the average AKS score was 96.1 points and remained essentially unchanged at 2 years (96.3 points). The mean change from baseline of 53.6 and 54.2 points at 6 months and 2 years, respectively, indicates that the majority of the improvement due to treatment had occurred by 6 months. Ninety-three percent (83/89 knees with a scorable AKS, 93%) of the patients had an excellent two year AKS score (≥ 90 points).
- Knee flexion was primarily regained by the 6-month interval (average 123.5°) and this magnitude of flexion was also observed at 2 years.
- Pre-operatively, patients lacked 6.1° of extension which improved by 6 months to a mild flexion contracture (average 3.0°) and further improved to full extension at the final 2-year endpoint (average 0.6°).
- Pre-operatively, 93% of patients had moderate to severe pain. At six months 98.8% of patients had no or mild pain: specifically, 62/83 (75%) had no pain, 20/83 (24%) had mild pain, 1/83 (1%) had moderate-occasional pain, and no patients had either moderate-continual or severe pain. At two years, 96% patients had no or mild pain: specifically, 66/89 (74%) had no pain, 19/89 (24%) had mild pain, 4/89 (4%) had moderate-occasional pain, and no patients had either moderate-continual or severe pain.
- Pre-operatively, 92% of patients had optimal (<5mm) anteroposterior (A/P) stability, at 6 months and 2 years optimal A/P stability was reported for 92% and 98% of patients, respectively.

Table 3: AKS Score for ATTUNE Knees with Minimum 2-Year Follow-up

SUMMARY	STATISTIC OR LEVEL	Pre-Op N=86 knees	6 Month Post-Op N=86 knees	6 Month Change from Baseline N=81 knees	2-Year Post-Op N=89 knees	2-Year Change from Baseline N=86 knees
AKS Score	Mean (SD)	42.4 (15.8)	96.1 (7.5)	53.6 (18.1)	96.3 (7.3)	54.2 (17.3)

Table 4: AKS Pain Sub-score for ATTUNE Knees with Minimum 2-Year Follow-up

SUMMARY	STATISTIC OR LEVEL	Pre-Op N=86 knees	6 Month Post-Op N=83 knees	6 Month Change from Baseline N=84 knees	2-Year Post-Op N=89 knees	2-Year Change from Baseline N=86 knees
AKS Pain Score	Mean (SD)	12 (10.4)	48.1 (4.5)	35.7 (11.3)	47.2 (6.9)	35.5 (12.3)

Table 5: Knee Flexion for ATTUNE Knees with Minimum 2-Year Follow-up

SUMMARY	STATISTIC OR LEVEL	Pre-Op N=90 knees	6 Month Post-Op N=84 knees	6 Month Change from Baseline N=82 knees	2-Year Post-Op N=100 knees	2-Year Change from Baseline N=90 knees
Flexion [Degrees]	Mean (SD)	116.4 (11.1)	123.5 (9.8)	6.8 (10.2)	123.7 (11.0)	7.8 (10.1)

Table 6: Knee Extension for ATTUNE Knees with Minimum 2-Year Follow-up

SUMMARY	STATISTIC OR LEVEL	Pre-Op N=89 knees	6 Month Post-Op N=91 knees	6 Month Change from Baseline N=86 knees	2-Year Post-Op N=100 knees	2-Year Change from Baseline N=89 knees
Extension [Degrees]	Mean (SD)	6.1 (5.5)	3.0 (3.3)	-3.0 (6.0)	0.6 (1.9)	-5.8 (5.8)

ADVERSE EVENTS (AE)

A summary of all adverse events (both systemic and local/surgical site) for the 782 ATTUNE Knees which have been reported are presented below. Device-relatedness (as reported by the surgeon), and the tally of adverse events which met the definition of serious (also as reported by the surgeon) are summarized for each adverse event category.

Table 7: Summary of Reported Adverse Events

AE Type (Systemic or Operative Site/Local)	Timing	Met the Definition of Serious?			Total
		Yes	No	Incomplete Information	
LOCAL / OPERATIVE SITE	Intra-operative	0	0	1	1
	Post-operative	18	11	2	31
SYSTEMIC	Post-operative	12	20	4	36
Grand Total		**30**	**31**	**8**	**68**

Systemic Adverse Events

The most common systemic adverse events were 'musculoskeletal', which included a variety of other orthopaedic conditions including contralateral TKA, total hip arthroplasty (THA) surgery, spine fusion, etc.

Operative Site/Local Adverse Events

There was one intra-operative, local AE: a tibial bone fracture was observed during cementation. Post-operatively, 31 local/surgical site AEs were reported. A *DePuy Synthes Companies of Johnson & Johnson* Medical Director classified these 32 AEs to facilitate summary (Table 8) and interpretation.

Table 8: Summary of Intra-operative and Post-operative, Operative Site/Local Adverse Events

Type/Classification of AE	Tally	Percent of AEs	Percent of Knees
Intra-operative AEs, sub-total = 1			
Bone Fracture	1	3.1%	0.1%
Post-operative AEs, sub-total = 31			
Joint Disorder (Stiffness)	10	31.3%	1.3%
Infection	6	18.8%	0.8%
Trauma	5	15.6%	0.6%
Bone Fracture	3	9.4%	0.4%
Pain	3	9.4%	0.4%
Dermatological	2	6.3%	0.3%
Aseptic Loosening	1	3.1%	0.1%
Hematoma	1	3.1%	0.1%
Grand Total=32			

REVISIONS

There have been 4 revisions among 782 ATTUNE Knees, of which polyethylene swaps were performed for 2 knees (Table 9).

Table 9: Detailed Information on Revisions

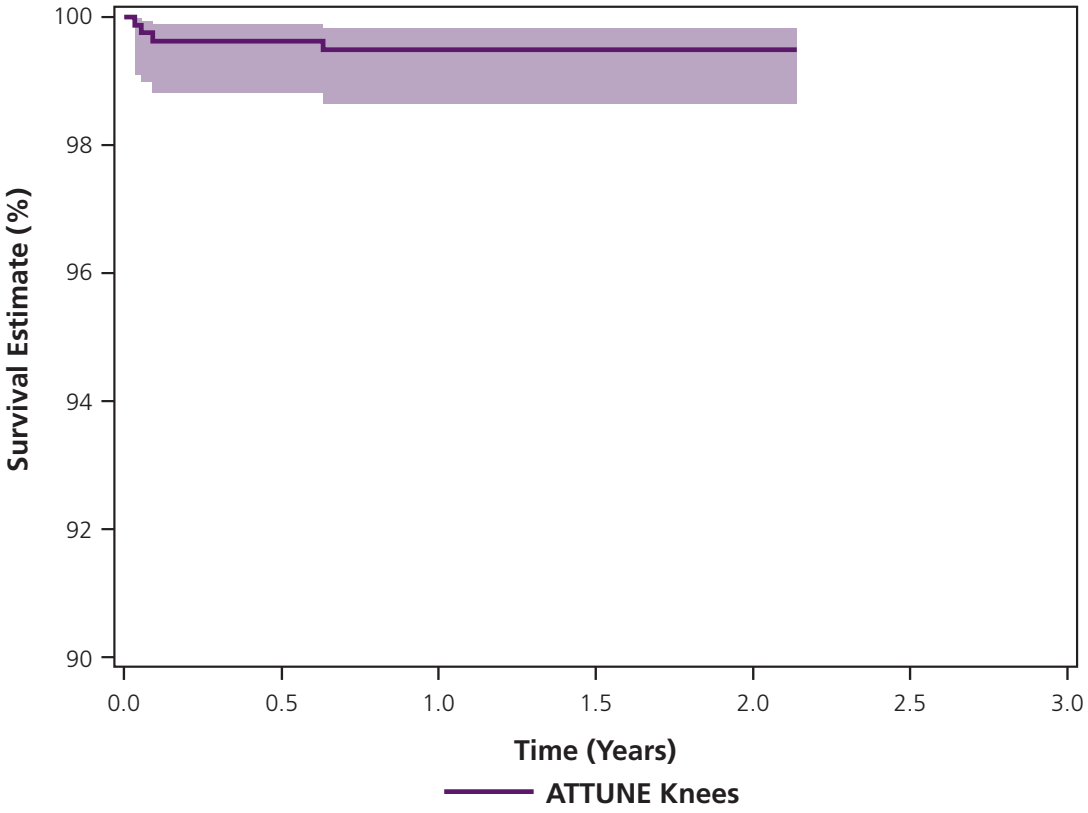
SUBJECT	# Days Until Revision	Revision Reason	Treatment, Components Removed	Serious*	Device Related*
001-05072-K1	21	INFECTION	I & D, Polyethylene insert swapped	Yes	Possibly
013-01413-K1	34	PERIPROSTHETIC FRACTURE[1]	Tibial base and femoral component	Yes	Definitely Not
017-03483-K1	231	ASEPTIC LOOSENING[2]	Tibial base and femoral component	No	Definitely Not
017-03569-K2	13	INFECTION	I & D, Polyethylene insert swapped	Yes	Definitely Not

* Serious and device-relatedness are reported by the investigator

1. A supracondylar femur fracture was observed. It is not possible to detect whether the crack initiated intra-operatively or post-operatively. The patient had severe osteopenia and a valgus deformity pre-operatively.
2. The surgeon attributed the loosening to 'operator error' associated with difficulty during cementation (doughy cement).

A Kaplan-Meier (KM) Survivorship analysis was completed to estimate survivorship of the primary TKA at 2 years post-operatively; revision was defined as the removal of any TKA component for any reason. For subjects who were revised, the time to revision was the date of revision minus the date of primary TKA. Consistent with the methodology of time to event analysis among some registries (e.g., methodology utilized by the UK NJR), the time to censoring for subjects who were not revised was defined to be the time of data extract (January 31, 2014) or death, whichever occurred first, minus the date of primary TKA. Results of this Kaplan-Meier survivorship analysis are presented in Figure 2 below. The 2-year KM survival estimate was 99.49% at 2 years (95% C.I.: 98.64%- 99.81%). This can also be expressed as 0.26 revisions per 100 component years (95% C.I.: 0.095 – 0.68).

Figure 2: Kaplan-Meier Survivorship Curve with 95% Confidence Interval (C.I.) Shaded Survival Estimate was 99.49% at 2 Years (95% C.I.: 98.64%- 99.81%), Reasons for Revision are Described Above



Treatment		Time (Years)			
		0	1	2	3
ATTUNE Knee	Survival Estimate	100.0	99.5	99.5	
ATTUNE Knee	Lower 95% Confidence Limit	100.0	98.6	98.6	
ATTUNE Knee	Upper 95% Confidence Limit	100.0	99.8	99.8	
ATTUNE Knee	Knees Remaining [a]	782	777	181	<40
ATTUNE Knee	Cumulative Number Observed [b]	0	4	4	4

a) **Knees Remaining** is defined to be the number of unrevised knees with a censoring time (time from date of primary TKA until date of extract or death) beyond the indicated time period.

b) **Cumulative number observed** is the number of revisions which have occurred prior to the indicated time period.

DISCUSSION

The ATTUNE Knee Early Performance Registry demonstrated satisfactory early clinical results for the ATTUNE Knee System. Overall, there was a marked improvement in outcomes as demonstrated by the positive change from baseline scores. Such improvements are expected with primary TKA surgery. The mean values of the AKS score, flexion and extension are consistent with reported values in the literature for primary TKA and the 'excellent' AKS scores at 2 years are encouraging. By 6 months, patients regained their pre-operative flexion. Between 6 months and 1 year, additional improvement in flexion was achieved with minimal, incremental improvement at the 2-year endpoint. Similarly, pre-operative flexion contractures were addressed: on average, pre-operative flexion contractures were halved by 6 months, and further improved to full extension at the final 2-year endpoint. The motion (magnitude of flexion, change from pre-op flexion, rate of return of flexion/extension) coupled with the high percentage of optimal post-operative A/P stability and the absence of adverse events related to instability, support the design goal to deliver motion and stability for patients. While satisfaction is multifactorial, the excellent AKS scores combined with the high percentage of patients with none/mild pain are encouraging clinical outcomes since these factors have been linked with primary TKA patient satisfaction.[1-4,6-7]

The type and frequency of adverse events is consistent with primary TKA.[8-10] Within the Safety Dataset (N=782 knees) there have been 4 revisions (2 infections treated with Irrigation & Debridement and prophylactic polyethylene swaps, 1 supracondylar femur fracture and 1 tibial loosening secondary to surgical error with doughy cement) reported in the Early Performance Registry across these 15 sites out to the 2-year time point. The 2-year survivorship estimate for the ATTUNE Knee Early Performance Registry was 99.49% at 2 years (95% C.I.: 98.64%- 99.81).

Strengths associated with this data include: prospective data collection with the *DePuy Synthes Companies of Johnson & Johnson* registry on 100 TKAs, and multi-center data coming from experienced surgeons/clinical researchers who had a commitment to studying all knees since initial product introduction which included possible learning curve. Weaknesses included: due to the planned, phased introduction of the product, the initial data was collected by surgeons with a conflict of interest (design surgeons).

It is important to note that the reported results are only reflective of the early post-operative phase and additional surveillance of longer-term performance will be ongoing via passive and active post market surveillance per company procedures, including but not limited to multiple ongoing multi-center studies, investigator initiated studies and outcomes registries worldwide.

REFERENCES:

1. Baker, P. N., van der Meulen, J. H., Lewsey, J., & Gregg, P. J. (2007). The role of pain and function in determining patient satisfaction after total knee replacement. Data from the National Joint Registry for England and Wales. *Journal of Bone & Joint Surgery* (Br), 89-B, 893-900.

2. Dunbar, M. J., Richardson, G., & Robertsson, O. (2013). I can't get no satisfaction after my total knee replacement: rhymes and reasons. *Bone & Joint Journal*, 95-B, 148-152.

3. Jacobs, C. A. & Christensen, C. P. (2014). Factors influencing patient satisfaction two to five years after primary total knee arthroplasty. *Journal of Arthroplasty*, 29, 1189-1191.

4. Scott, C. E., Howie, C. R., MacDonald, D., & Biant, L. C. (2010). Predicting dissatisfaction following total knee replacement: a prospective study of 1217 patients. *Journal of Bone & Joint Surgery* (Br), 92, 1253-1258.

5. *DePuy Synthes Companies* Internal Statistical Report #7532 (date of extraction 31 Jan 2014).

6. Noiseux, N. O., Callaghan, J. J., Clark, C. R., Zimmerman, M. B., Sluka, K. A., & Rakel, B. A. (2014). Preoperative predictors of pain following total knee arthroplasty. *Journal of Arthroplasty*, 29, 1383-1387.

7. Williams, D. P., O'Brien, S., Doran, E., Price, A. J., Beard, D. J., Murray, D. W. et al. (2013). Early postoperative predictors of satisfaction following total knee arthroplasty. *Knee*, 20, 442-446.

8. Dalury, D. F., Pomeroy, D. L., Gorab, R. S., & Adams, M. J. (2013). Why are total knee arthroplasties being revised? *Journal of Arthroplasty*, 28, 120-121.

9. Healy, W. L., Della Valle, C. J., Iorio, R., Berend, K. R., Cushner, F. D., Dalury, D. F. et al. (2013). Complications of total knee arthroplasty: standardized list and definitions of the Knee Society. *Clinical Orthopaedics and Related Research*, 471, 215-220.

10. Sharkey, P. F., Lichstein, P. M., Shen, C., Tokarski, A. T., & Parvizi, J. (2014). Why Are Total Knee Arthroplasties Failing Today-Has Anything Changed After 10 Years? *Journal of Arthroplasty*, 29, 1774-1778.

DePuy Synthes
COMPANIES OF Johnson&Johnson
People inspired™

DePuy Orthopaedics, Inc.
700 Orthopaedic Drive
Warsaw, IN 46582
Tel: +1 (800) 366-8143

DePuy (Ireland)
Loughbeg Ringaskiddy
Co. Cork
Ireland
Tel: +353 21 4914 000
Fax: +353 21 4919 149

www.depuysynthes.com