

**PMA MEMORANDUM**

**To:** P000057/Original, Amendments A1, A2, A3, A5, and A6

**From:** John S. Goode, Biomedical Engineer, FDA/CDRH/ODE/DGRD/ORDB

**Subject:** Ascension MCP, metacarpophalangeal total joint prosthesis

**Sponsor/Manufacturer:** Ascension Orthopedics, Inc.  
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**Date:** July 11, 2001

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**CLINICAL REVIEW: THIS REVIEW MEMO CONTAINS INFORMATION ABOUT:**

- Clinical Data Development History;
- Description of Patients;
- Case Series Analysis: (This is the sponsor's analysis presented in Amendments 3 and 5. This is the analysis that will be focused on by FDA and the sponsor at the Panel Meeting.);
- Adverse Events Reported in the Case Series Analysis (Amendments 3 and 5) and in the Original PMA. (This information will also be focused on by FDA at the Panel Meeting.);
- Summary of Sponsor's Original PMA Clinical Data Analysis;
- Summary of Major Deficiencies Identified by FDA in the Original PMA;
- Summary of Sponsor's Clinical Data Analysis in Amendment 2;
- Summary of Major Deficiencies Identified by FDA in Amendment 2; and
- Brief Summary of Literature Information on Alternative Treatments: Information Contained in the Original PMA and Amendment 3.

**The clinical information was contained in the following submissions from Ascension Orthopedics to FDA:**

- PMA: P000057 (Volumes 1 to 13); and
- Amendment 1: Contains 3 tables outlining follow-up information for key endpoints for pyrocarbon MCP joint device patients and literature controls.
- Amendment 2: Contains responses to FDA's letter dated February 23, 2001 including a non-inferiority analysis comparing the study device with literature for Swanson Silicone Spacer.
- Amendment 3: Contains responses to FDA's letter dated May 1, 2001 including case series safety and effectiveness analysis (Note: For RA patients, analysis was limited to 1 to 5 year treatment outcome).
- Amendment 5: Contains a longer-term analysis for RA patients to supplement information provided in Amendment 3.
- Amendment 6: Contains the sponsor's Summary of Safety and Effectiveness Data (SSED) and Proposed Instructions for Use.

**CLINICAL DATA DEVELOPMENT HISTORY:**

Between 1979 and 1987, 151 pyrolytic carbon MCP implants were put in 53 patients at the Mayo Clinic by Drs. Beckenbaugh and Linscheid. Of these, 147 implants were primary ball-and-cup uncemented pyrocarbon implants; 2 were condylar pyrocarbon implants (implants with a conical shaped bump in the center of the articulating surface of the distal component that interfaced with a groove on the proximal component's articulating surface); and 2 were revision ball-and-cup pyrocarbon implants (one uncemented and one cemented).

The 53 patients who received 147 primary ball-and-cup uncemented pyrocarbon implants represent the case series upon which the clinical data in this PMA is based. The outcome of the other 4 pyrocarbon implants (2 condylar and 2 revision) are mentioned in the Module 1 and PMA Volume 1 of 13 but are not summarized as part of the clinical data in this PMA or factored into the success/failure criteria for the 53 patients.

In 1992, Ascension Orthopedics, Inc. was founded by Drs. Klawitter and Cook and Ascension Orthopedics, Inc. is the sponsor of this PMA submission. The sponsor worked with Dr. Beckenbaugh to refine certain aspects of the prosthesis design, resulting in the Ascension® MCP device. The Ascension MCP device is not the one that was used in the animal or clinical study but is the device for which Ascension Orthopedics is requesting approval in their PMA. Similarities and differences between the pyrocarbon implant used in the animal and clinical studies and the Ascension MCP are presented in the pre-clinical review memo. The pre-clinical review memo also includes a device description, identification of material properties, and a summary of animal testing, *in vitro* mechanical testing, finite element (FEA) stress and strain examinations, and material biocompatibility evaluations.

Drs. Beckenbaugh and Linscheid did not consider themselves investigators or the Mayo Clinic an investigational site when they were implanting the pyrocarbon MCP finger joint devices. The sponsor stated that a prospective clinical investigation was not performed. Therefore, there was no prospective protocol or case report forms for the implantation of the 53 patients. The sponsor conducted a retrospective study by completely reviewing the medical records of each patient who received the MCP at Mayo Clinic.

**INDEPENDENT AUDIT OF THE DATA:**

Information provided in the Original PMA and Amendments 1 and 2 in support of the safety and effectiveness of the Ascension MCP is based on an independent report from a contract research organization (CRO), Boston Biostatistics, Inc. (BBI). BBI audited and validated the accuracy and completeness of the clinical records, extracted the information into computerized databases and analyzed the data. In addition, they performed an extensive review of the medical literature, established an appropriate literature control, and analyzed the Ascension MCP data compared to the control.

Please note: The information in Amendments 3 and 5 was not collected or analyzed by the CRO (BBI) but by Ascension Orthopedics, Inc.

**DESCRIPTION OF PATIENTS:**

From 12/79-2/87, 151 pyrolytic carbon MCP implants were put in 53 patients. Of these, 147 implants were primary ball-and-cup uncemented pyrocarbon implants; 2 were condylar pyrocarbon implants; and 2 were revision ball-and-cup pyrocarbon implants (one uncemented and one cemented).

The sponsor provided the following table containing information about the number of patients in which Drs. Beckenbaugh and Linscheid implanted pyrocarbon MCP joints, the number of procedures performed, the date of first and last procedure, and the total number of implants. Again, please note that only 147 primary uncemented ball-and-cup pyrocarbon MCP devices of the total 151 pyrocarbon MCP devices implanted represent the case series upon which the clinical data in this PMA is based:

	Dr. Beckenbaugh	Dr. Linscheid	Total
Number of Patients	32	21	53
Number of Procedures	39	22	61
Date of First Procedure	12/17/79	1/8/81	12/17/79
Date of Last Procedure	5/30/85	2/26/87	2/26/87
Number of Implants	101	50	151

Notes: 6 patients had bilateral surgery during a second procedure; 2 patients had 1 primary pyrocarbon MCP implant that was revised to a second pyrocarbon MCP implant during a second procedure. Thus, the total number of procedures exceeds the total number of patients.

**Inclusion/Exclusion Criteria for Retrospective Clinical Data:**Inclusion Criteria:

- MCP joint exhibited pain, deformities, and/or limited function
- There was radiographic evidence of arthrosis of the MCP joint
- The patient consented to receive a new "custom" implant after the potential risks and hazards and the potential benefits of the new device with unknown long term results were explained.
- In the physician's judgment, the patient might benefit from use of the device

Exclusion Criteria:

- None identified

**Demographics:**

	All Diagnoses	OA/Trauma	RA/SLE
Age (years)	57.5 (Range: 21 – 78)	54.9 (Range: 21 – 77)	58.0 (Range: 35 – 78)
Gender	45 Female, 8 Male	1 Female, 7 Male	44 Female, 1 Male
Diagnosis			
OA	3 (6%)	3 (38%)	-
Trauma	5 (9%)	5 (62%)	-
RA	44 (83%)	-	44 (98%)
SLE	1 (2%)	-	1 (2%)
Time from Diagnosis to First Pyrolytic Carbon Implant Surgery*	195.8 months (Range: 36 – 432 months) (N=40)	-	195.8 months (Range: 36 – 432 months) (N=40)

\* It is important to note that most of the patients had lived with their RA/SLE disease for a very long time and the disease was fairly advanced in many. Therefore, the sponsor stated that for many of the patients, treatment expectations were limited and realistic.

Sponsor provided additional information in the PMA regarding:

- Patient demographics stratified by hand dominance, surgeons;
- Medical History;
- Non-implanted hand and finger pre-pyrolytic carbon implant surgery procedures;
- Wrist and thumb history;
- Elbow history;
- Non-hand total joint arthroplasty history-procedures

**Treatment:**

	All Diagnoses	OA/Trauma	RA/SLE
Number of Patients	53	8	45
Number of Hands	60	9	51
Number of Implants	151	11	140
Primary	147	9	138
Revision	2	1	1
Condylar	2	1	1
Number of Patients w/			
1 Primary Implant	17	7	10
2 Primary Implants	12	1	11
3 – 8 Primary Implants	24	0	24

Non-Pyrolytic Carbon Finger Implants:

6 patients received 25 other, non-pyrolytic carbon finger (non-thumb) implants prior to receiving pyrolytic carbon MCP implants. 24/25 of these implants were put into hands that would not receive a future pyrolytic carbon implant. The remaining MCP implant (a silicone spacer) was inserted into a hand that later received a pyrolytic carbon implant, however, the pyrolytic carbon implant was placed in a different

finger. So, all of the pyrolytic carbon implants were put into fingers that had never received another type of joint replacement device (other than the 2 pyrolytic carbon revision implants of primary pyrolytic carbon devices).

**Mean Follow-Up Time (in months) for Primary MCP Pyrolytic Carbon Implants by Diagnostic Category:**

		All Diagnoses	OA/Trauma	RA/SLE
Patients	N	53	8	45
	Mean	102.6 months	107.4 months	101.8 months
	Min, Max	1.7, 206 months	1.7, 191.7 months	8.1, 206.0 months
Implants	N	147	9	138
	Mean	93.1 months	112.6 months	91.8 months
	Min, Max	0.9, 206 months	1.7, 191.7 months	0.9, 206.0 months

**Proportion of Patients Followed Over Time:**

Follow-Up Time (mo)	Cumulative Deaths	Patients Left	Still Followed	% Followed
0	0	53	53	100%
>3	0	53	52	98.1%
>6	0	53	51	96.2%
>9	0	53	50	94.3%
>12	0	53	49	92.5%
>18	0	53	41	77.4%
>24	3	50	41	82%
>60	6	47	38	80.9%
>120	13	40	29	72.5%

The Tables provided in Amendment 1 to the PMA contain a better description of the amount of follow up information on these 53 patients over time. Table 3 in Amendment 1 contains information about the amount of follow-up data for some of the clinical and radiographic endpoints over the course of the study.

**Panel Please Note:**

**There will be a panel question regarding whether the data support each of the proposed indications for use or a more specific list of indications for use.**

**Proposed Indications for Use for the Ascension MCP (revised in Amendment 3):**

The Ascension® MCP is intended for use as a total joint replacement of the index, long, ring, and small finger metacarpophalangeal (MCP) joints that exhibit symptoms of pain, limited range of motion, or inadequate bony alignment (i.e., subluxation or dislocation) secondary to articular destruction or degenerative disease related to rheumatoid arthritis, systemic lupus erythematosus, osteoarthritis, or post-traumatic arthritis where soft tissue reconstruction provides stabilization.

**Notes Regarding Indications for Use:**

- Currently, the indications for use does not exclude revision procedures; and
- The sponsor stated that in some cases, the collateral ligaments about the MCP joints are damaged or disrupted by disease or preparation of the articular surfaces for the implant during surgery. These ligaments may or may not be repairable. Even in cases where they are not repairable, a ball-and-cup implant may still result in a stable reconstruction if the width of the prosthesis provides enough distraction to increase the tension in the soft tissue envelope about the prosthesis (capsule, skin, tendons, tendon sheath, volar plate). In these situations, the Ascension MCP device can be used. Therefore, a lack of collateral ligaments does not in itself constitute a contra-indication for the subject device. However, the surgeon judgement regarding the capability of the surrounding soft tissue envelope to provide a stable reconstruction is required. Therefore, in Amendment 3 the sponsor

revised the indications for use to include the phrase: "where soft tissue reconstruction provides stabilization."

**Alternative practices and procedures:**

The sponsor stated that early conservative treatment includes joint injections, NSAIDs, avoidance of heavy stress, Coban wrapping and/or splinting. Surgical treatment may restore some ROM and is typically used when conservative measures no longer give relief. Surgical treatment may include fusion of the bones, interposition arthroplasty with tendon or joint replacement surgery with a silicone or rubber spacer implant.

**CASE SERIES ANALYSIS: (THIS IS THE SPONSOR'S ANALYSIS PRESENTED IN AMENDMENTS 3 AND 5. THIS IS THE ANALYSIS THAT WILL BE FOCUSED ON BY FDA AND THE SPONSOR AT THE PANEL MEETING.)**

Note: In the original PMA and Amendments 1 and 2, the sponsor performed a clinical data analyses for the Ascension MCP. These analyses and their apparent shortcomings are summarized later in this review memo. The case series analysis provided by the sponsor in Amendments 3 and 5 is the analysis that will be focused on by the FDA and the Sponsor at the Panel Meeting.

**Summary:**

In the sponsor's case series analysis of their data, presented in Amendments 3 and 5 of the PMA, the sponsor determined that the patients can be stratified and effectively evaluated based on two baseline medical conditions: (1) osteoarthritis/post traumatic patients (OA/Trauma); and (2) rheumatoid arthritis/systemic lupus erythematosus patients (RA/SLE). Retrospective success/failure criteria with respect to device effectiveness endpoints (including criteria for implanted joint pain, joint function, and radiographic data) and success/failure criteria with respect to device safety endpoints (implant loosening, removal, dislocation, and post-operative implant fracture) were established. Separate success/failure criteria were defined for the OA/Trauma and RA/SLE patient groups (for the RA/SLE group, retrospective effectiveness criteria were defined for a 1-5 year treatment outcome analysis (in Amendment 3) and a longer-term treatment outcome analysis (in Amendment 5)). Each implant was determined to be either excellent, good, unsatisfactory, or indeterminate. Each implant with an excellent or good outcome was considered a success while an implant with an unsatisfactory outcome was considered a failure. Patients lacking information required as part of the definition of success and failure were termed to be indeterminate. Because the sponsor did not summarize the frequency and severity of all of the adverse events for the 53 case series patients in their analysis in Amendments 3 and 5, the sponsor's earlier summary in the Original PMA was used to evaluate overall device safety.

With case series, the investigator does not control treatment assignment, endpoint ascertainment, selection biases, or confounding factors. Case series are typically used to generate hypotheses, not to test them.

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**Panel Please Note:**

**There will be a panel question regarding overall device effectiveness.**

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**OA/Trauma Patients:**

The sponsor stated that the OA/Trauma patients presented with damaged or destroyed articular surfaces and almost always had pain and limited motion. Most OA/Trauma patients needed treatment in only one MCP joint; only one patient required treatment at more than one MCP joint. In these cases, the physician had the following expectations for total joint arthroplasty of the MCP joint:

**Physician's Expectation for OA/Trauma (Treatment Objective):**

Relieve pain, maintain reasonable joint range of motion (ROM), and maintain joint reduction

The sponsor stated that these expectations are typical for assessment of state-of-the-art total joint replacement devices used in arthroplasty treatment of the hip and knee. Based on these physician expectations, the following criteria have been set to assess the effectiveness of the Ascension MCP:

**OA/Trauma Effectiveness Criteria:**

The following effectiveness criteria were applied on an implant basis to determine the treatment outcome category for each implant. Please note that the sponsor's success/failure criteria were retrospectively defined. An implant with an Excellent or Good outcome is considered a Success while an implant with an Unsatisfactory outcome is considered a Failure.

Excellent

1. Physical exam, ROM and radiographic data > 2 years indicating:
  - a. Pain free implant at last follow-up;
  - b. Increase in range of motion (ROM) from baseline, or ROM > 50 degrees and
  - c. Reduced implant position.

Good

1. Physical exam, ROM and radiographic data < 2 years indicating:
  - a. Increase in ROM from baseline, or ROM > 50 degrees; and
  - b. Reduced implant position; and
2. Physical exam or telephone conversation with a physician > 2 years indicating:
  - a. Pain free implant; and
  - b. Implant survival

Unsatisfactory

1. Implant related pain at last follow-up;
2. Implant loosening or removal;
3. Post-operative implant fracture;
4. Decrease in ROM from baseline with ROM < 50 degrees; or
5. Implant subluxation or dislocation.

Indeterminate

1. No information > 2 years or insufficient information > 2 years to indicate maintenance of the improvements.

**Implant Safety Criteria for the OA/Trauma Case Series:**

The frequency and severity of the following events were evaluated for purposes of determining device safety:

1. Intraoperative implant fracture
2. Non-intraoperative implant fracture
3. Unstable intraoperative bone fracture
4. Post operative bone fractures
5. Implant related infection
6. Adverse biological reaction to implant

**OA/Trauma Implant Treatment Outcomes:**

(Range of last follow-up time point for patients determined to be successes 3.5 to 17 years)

OA/Trauma Implant Treatment Outcomes:**	Patients	Implants	Hands	Comment
Number of Implants	8	9	9	-
Successful Implants	6/8 (75%)	7/9 (78%) (6 excellent, 1 good)	7/9 (78%) (6 excellent, 1 good)	-
Implants Determined to be Failures	1/8 (12.5%)	1/9 (11%)	1/9 (11%)	Loosening: 1/9 at 1.1 years (revised with a new pyrocarbon implant with cement)*;
Implants for which an Outcome was Indeterminate	1/8 (12.5%)	1/9 (11%)	1/9 (11%)	-

\* Note: No other implants in the OA/Trauma cohort were removed.

\*\* Note: Success/Failure/Indeterminate criteria were retrospectively defined.

Summary of Additional Information from the OA/Trauma case series:

One of these patients (patient #43) was a Trauma patient and had an intraoperative fracture during primary implantation. The fractured component had to be removed by drilling it out of the bone. A new pyrocarbon implant was inserted. This implant was revised at 1.1 years for loosening. It was revised to a new pyrocarbon implant with cement. Histopathologic exam of subcutaneous tissue stained with carbonaceous debris due to removal of the fractured proximal component during primary surgery revealed chronic proliferative synovitis. The histopathologist, in his summary report, stated that there were no inflammatory cells and no cellular reaction to the carbon particles. He concluded by stating that the sections showed proliferative synovitis but it was not a reaction to the carbon particles.

The 6 implants that had an Excellent outcome had last follow-ups ranging from 3.5 to 16.0 years, and all but 1 implant (patient #34) demonstrated an increase in ROM. For patient #34, the post-operative ROM was very good at 65 degrees. The 1 implant with a Good outcome had a last follow-up indicating implant survival at 17 years, while the implant with Indeterminate outcome had 0.5 years follow-up demonstrating good improvement. All implants demonstrated no joint pain at long-term follow-up except for the unsatisfactory implant in patient #43 that had pain secondary to loosening.

**OA/Trauma Safety Results:**

Safety Issue	Number	Outcome
Intraoperative Implant Fracture During Implantation	2 implants in 2 patients	Both had fractured implant removed and new pyrocarbon implant inserted
No other safety issues*		

\* The sponsor reported no other safety issues for the OA/Trauma patients in Amendment 3. However, what the sponsor means is that there were no other reported occurrences of the implant safety criteria listed above. In fact, there were many other adverse events for the OA/Trauma and RA/SLE patients. These events were described in the Original PMA and are summarized later in this review memo.

**RA/SLE Patients**

The RA/SLE patients presented with damaged or destroyed articular surfaces and many had limited extension, pain, and dislocated joints. Almost all patients had multiple joint involvement. With these cases, in the presence of a progressive disease, and faced with an unknown rate of disease progression and probable continued soft tissue degradation, the physician normally had realistic and limited expectations. Unlike with OA/Trauma patients who had generally healthy soft tissue structures that could provide stability and motion, the expectation for the RA/SLE patients was patient and joint specific, and dependent on the baseline MCP joint conditions. At best, the expectation for the RA/SLE patient was equivalent to

that for the OA/Trauma patients, i.e., a long term, pain free, stable (reduced) implant. More often, the treatment objective for the RA/SLE patient was tempered with the knowledge of each patient's existing medical condition and probable course of disease evolution. Therefore, the expectations for total joint arthroplasty of the MCP joint in the RA/SLE patients were:

**Physician's Expectation for RA/SLE (Treatment Objective):**

- A. In cases with limited extension (a.k.a., extension lag or extension deficit), the primary expectation was to increase extension.
- B. In cases with pain, the primary expectation was to relieve pain.
- C. In cases of a destroyed or eroded articular surface, the primary expectation was to replace the eroded surfaces and provide a reduced joint.
- D. In cases with a pre-operative dislocation, the primary expectation was to provide a reduced joint.
- E. In cases presenting a combination of conditions A, B, C, and/or D, the primary expectation was a comprehensive combination of the primary expectations for each of the individual conditions. For example, in case with limited extension and pain (A + B), the primary expectation was to increase extension and relieve pain.

Note: The sponsor stated that the physician expectations were derived from the pre-op surgeon's notes and physical exam records.

The sponsor had the following rationale for evaluating effectiveness criteria on an implant, rather than patient, basis; 1 year evaluation time point; and RA/SLE patient serving as their own control:

"As indicated below, an excellent outcome required an improvement in all primary treatment expectations, as well as a pain free joint and a reduced joint position, regardless of the baseline conditions. Further, the improvement must be supported with objective clinical findings greater than 1 year. A good outcome again required improvement in the primary treatment expectations, a pain free joint and reduced joint; however, objective findings of less than 1 year were acceptable if supported by more subjective data greater than 1 year. In addition, due to inconsistent disease progression within a given hand and patient, the soft tissue structures surrounding some implants would be more affected than tissues around another implant. Thus, outcomes could vary widely even across multiple implants in a patient with multiple joint involvement and treatment. Therefore, effectiveness criteria are more appropriately evaluated on an implant basis as opposed to a patient basis. Further, since the disease can progress and the soft tissues degrade unabated at an unknown rate, 1 year has been set as the minimum amount of time that the surgical improvement must be maintained. Although, many patients will see improvements maintained for greater than 1 year, 1 year is a reasonable expectation. Finally, because the RA/SLE patient population had advanced disease condition, and there was no chance of spontaneous recovery without non-conservative treatment, and because the treatment expectation was based on individual patient and joint conditions, patients served as their own control."

Based on these physician expectations and in light of patients having a remittent progressive disease acting as self-controls, the following criteria have been set to assess the effectiveness of the Ascension MCP:

**RA/SLE Effectiveness Criteria (1 to 5 Year Evaluation):**

The following effectiveness criteria were applied on an implant basis to determine the treatment outcome category for each implant. Please note that the sponsor's success/failure criteria were retrospectively defined. An implant with an Excellent or Good outcome is considered a Success while an implant with an Unsatisfactory outcome is considered a Failure.

Excellent

1. Physical exam, ROM data, and radiographic data > 1 year indicating:
  - a. Improvement of all treatment objectives;

- b. Pain free joint; and
  - c. Reduced implant position
2. Subjective or objective information indicating a reduction in the improvement of treatment objectives after 5 years is acceptable.

(Note: What is meant by criterion #2 is that if there was a negative report ("reduction of the improvement") of one of the treatment objectives (i.e., A, B, C, D, or E summarized above) after 5 years, the patient may still be considered excellent. A negative report after 5 years of implantation does not penalize the study device in terms of success.)

#### Good

1. Physical exam, ROM data, and radiographic data < 1 year<sup>2</sup> indicating:
  - a. Improvement of all treatment objectives;
  - b. Pain free joint; and
  - c. Reduced implant position; and
2. Subjective or objective information (a physical exam at another clinic (orthopedic, rheumatology, etc.), radiographic data, a questionnaire or telephone conversation with a physician) at > 1 year indicating:
  - a. maintenance of the improvements; or
  - b. implant survival.
3. Subjective or objective information indicating a reduction in the improvement of treatment objectives after 5 years are acceptable.

(Note: What is meant by criterion #3 is that if there was a negative report ("reduction of the improvement") of one of the treatment objectives (i.e., A, B, C, D, or E summarized above) after 5 years, the patient may still be considered good. A negative report after 5 years of implantation does not penalize the study device in terms of success.)

#### Unsatisfactory

1. Primary treatment objective(s) same or not improved by the surgery;
2. Implant related pain at last follow-up;
3. Implant loosening;
4. Implant removal < 5 years;
5. Implant dislocation < 5 years; or
6. Post-operative implant fracture

(Note: What is meant by criteria #4 and #5 is that if there is an implant removed or dislocated after 5 years, the patient may still be considered excellent or good. A device removal or dislocation after 5 years does not penalize the study device in terms of success.)

#### Indeterminate

1. No information > 1 year, or insufficient information > 1 year to indicate maintenance of the improvements at < 5 years

Note: Because the sponsor included the criteria: Excellent #2, Good #3, and Unsatisfactory #4 and #5, the sponsor is actually providing success/failure results from 1 to 5 years. The sponsor is not penalizing the subject device if there is a negative event (i.e., removal, dislocation, reduction in treatment objectives, pain, or reduction in implant position) after 5 years. The sponsor believes the 5-year criteria is appropriate for this patient population because the criteria acknowledge and accommodate the potential confounding influence on treatment outcomes of soft tissue attenuation and degradation related to the RA/SLE baseline medical condition.

Note: If a patient is a success at 1 year and then is lost to follow-up, that patient may still be considered a success (excellent or good).

Note: The sponsor stated that although a 1 year criteria was established for an implant to be considered a success (i.e., excellent or good outcome), as discussed in the following results section, 72% of the successful implants had > 2 years follow-up; 28% had < 2 years follow-up.

Note: Currently there is an ambiguity between the sponsor's definition for good and indeterminate with respect to knowledge about the maintenance of improvements (as compared to baseline). Because the sponsor defined criteria: Good #2 (a) or (b), good doesn't require knowledge of the maintenance of improvements. However, if there is insufficient information > 1 year to indicate maintenance of the improvements at <5 years, that is also to be categorized as indeterminate.

#### RA/SLE Implant Treatment Outcome (1 to 5 Year Evaluation)\*\*:

RA/SLE Implant Treatment Outcomes:*	Patient		Implants	Hands		Implants Removed
	All (n=38 patients)	Partial (n=7 patients)		All (n=45 Hands)	Partial (n=6 Hands)	
Number of Implants						-
Successful Implants	27/45 (60%)	6/45 (13%)	82/138 (59%) (48 excellent, 34 good)	30/51 (59%)	5/51 (10%)	6 of the 82 implants determined to be successful were removed in 2 patients; (4 at 5.5yrs; 2 at 11yrs): All replaced with silicone spacer**
Implants Determined to be Failures	8/45 (18%)	7/45 (16%)	37/138 (27%); 2 due to loosening	10/51 (20%)	6/51 (12%)	14 of the 37 implants determined to be failures were removed in 8 patients; (9 replaced with silicone spacers, 4 reinserted with bone cement, and 1 new pyrocarbon implant was inserted). See below for time of removal.
Implants for which an Outcome was Indeterminate	3/45 (7%)	2/45 (4%)	19/138 (14%)	5/51 (10%)	2/51 (4%)	

\* Note: Success/Failure/Indeterminate criteria were retrospectively defined.

\*\* Please note that because the sponsor included the criteria: Excellent #2, Good #3, and Unsatisfactory #4 and #5, the sponsor is actually providing success/failure results from 1 to 5 years.

- The sponsor is not penalizing the subject device if there is a negative event (i.e., removal, dislocation, reduction in treatment objectives, pain, or reduction in implant position) after 5 years. The sponsor believes the 5-year criteria is appropriate for this patient population because the criteria acknowledge and accommodate the potential confounding influence on treatment outcomes of soft tissue attenuation and degradation related to the RA/SLE baseline medical condition; and
- If a patient is a success at 1 year and then is lost to follow-up, that patient may still be considered a success (excellent or good).

**Summary of 1 to 5 year outcome analysis:**

A detailed summary of the treatment outcomes for implants in the RA/SLE patient cohort is provided in Amendment 3/Appendix 3. Forty-eight (48) implant outcomes were considered excellent with average last follow-up 8.3 years (range 1.0-16.8). Thirty-seven (37) of the 48 implants had last follow-up > 2 years and 11 of the 48 implants had last follow-up < 2 years. Thirty-four (34) implant outcomes were considered good with average last follow-up 5.9 years (range 1.2-13.6). Twenty-two (22) of the 34 implants had last follow-up > 2 years and 12 of the 34 implants had last follow-up < 2 years. Thus, 59 (72%) of the 82 successful implants had last follow-up greater than 2 years and 23 of the 82 successful implants had last follow-up less than 2 years.

The sponsor stated that on an intent to treat basis when all implanted devices are considered in determining success, 59% (82/138) of the implants had an Excellent or Good outcome and thus were considered successful. When only implants with a known outcome are considered (i.e, excluding indeterminate outcomes), 69% (82/119) of the implants were considered successful.

For implants demonstrating Excellent and Good outcomes, there were no reports of implanted joint pain at an average follow-up of 6.4 years (range 0.4 to 16.8 years), with 1 patient reporting hand pain at 10.0 years (patient #30). The average extension increase was 34.0 degrees (range - 20 to 125 degrees) at an average follow-up of 2.0 years (range 0.1 to 11.7 years). All patients with a primary treatment expectation of increasing extension showed an extension increase except for 2 implants (1 each in patients #31 and #44) that showed no increase, but had ROM > 40 degrees. Accordingly, these 2 implants had an outcome of Good. Five implants in 4 patients with a treatment expectation of joint reduction and/or surface replacement showed an extension decrease, but had good to excellent post-operative ROM averaging 29.0 degrees (range 20 to 50 degrees). Of the 82 implants considered successful, 77 had last follow-up radiographic data that showed 61(79%) implants reduced at an average of 3.9 years (range 0.1 to 12.9 years). Eleven implants were subluxed (average follow-up 7.0 range 1.4-13.0), and 5 were dislocated. Of the 5 dislocated implants, 4 were in one patient (#28) with 2 dislocations noted at 10.0 years and 2 more noted at 11.5 years, and 1 was in patient #8 noted at 11.0 years follow-up.

There were 6 implants removed from 2 patients in the excellent/good group; 4 implants were removed from patient #23 at 5.5 years due to disease related flexion contracture and ulnar deviation deformity, and 2 implants were removed from patient #8 at 11.0 years due to subluxation/dislocation related to soft tissue attenuation. All removed implants were successfully converted to a silicone spacer.

For the group of patients with an unsatisfactory outcome, 14 implants in 8 patients were removed. Two implants were removed due to loosening (patient #40 at 1.5 years and patient #33 at 4.9 years). The 12 other implants removed were revised due to disease related soft tissue degradation that resulted in flexion contracture (4 implants: 2 in patient #49 and 2 in patient #37), ulnar deviation deformity and dislocation (3 implants in patient #26), or subluxation/dislocation (5 implants: 1 in patient #15, and 2 each in #13 and #39). All removed implants were successfully revised; 9 were replaced with silicone spacers, 4 pyrocarbon implants were reinserted with bone cement, and 1 new pyrocarbon implant was inserted.

The other 23 implants in 8 patients with an unsatisfactory outcome were unsuccessful due to extension contractures (4 implants: 3 in patient #12 and the small in #39), lack of extension improvement or extension deficit (12 implants: 4 each in patients #24 and #35, and 2 each in patients #39 and #51), recurrent severe ulnar deformity (4 in patient #25) and dislocation (3 implants: 2 in patient #32 and 1 in patient #42). Thus, of the 37 implants in 15 patients with unsatisfactory outcomes, only 2 were directly related to implant loosening. All other unsatisfactory outcomes were due to disease related soft tissue degradation leading to loss of extension or joint location, or recurrent ulnar deformity.

**RA/SLE Effectiveness Criteria (Long Term Outcome Evaluation):**

In Amendment 5, the sponsor performed the following long-term outcome effectiveness analysis. The sponsor modified their previous criteria to eliminate the 5-year caveat. Again, please note that the sponsor's success/failure criteria were retrospectively defined. An implant with an Excellent or Good

outcome is considered a Success while an implant with an Unsatisfactory outcome is considered a Failure. The long-term outcome success/failure criteria (what the sponsor defined as the modified criteria) were defined as follows:

Modified Criteria:

Excellent

1. Physical exam, ROM data, and radiographic data > 1 year indicating:
  - a. Improvement of all treatment objectives;
  - b. Pain free joint; and
  - c. Reduced implant position

Good

1. Physical exam, ROM data, and radiographic data < 1 year indicating:
  - a. Improvement of all treatment objectives;
  - b. Pain free joint; and
  - c. Reduced implant position; and
2. Subjective or objective information (a physical exam at another clinic (orthopedic, rheumatology, etc.), radiographic data, a questionnaire or telephone conversation with a physician) at > 1 year indicating:
  - a. maintenance of the improvements; and
  - b. implant survival.

Unsatisfactory

1. Primary treatment objective(s) same or not improved by the surgery;
2. Implant related pain at last follow-up;
3. Implant loosening;
4. Implant removal;
5. Implant dislocation; or
6. Post-operative implant fracture

Indeterminate

1. No information > 1 year, or insufficient information > 1 year to indicate maintenance of the improvements

Note: Although a 1 year criteria was established for an implant to be considered a success (i.e., excellent or good outcome), as discussed in the following results section, 67% of the successful implants had > 2 years follow-up; 33% had < 2 years follow-up.

Note: Unlike the sponsor's 1 to 5 year analysis, in the sponsor's long term outcome analysis there is no ambiguity between the sponsor's definition for good and indeterminate with respect to knowledge about the maintenance of improvements (as compared to baseline). (See the 1 to 5-year analysis notes for more details).

**RA/SLE Implant Treatment Outcome (Long-Term Outcome Evaluation):**

Range of last follow-up time point for patients determined to be successes 1.0 to 16.8 years

RA/SLE Implant Treatment Outcomes:*	Patient		Implants	Hands		Implants Removed**
	45			51		
Number of Implants	All (n=38 patients)	Partial (n=7 patients)		All (n=45 Hands)	Partial (n=6 Hands)	
Successful Implants	17/45 (38%)	6/45 (13%)	51/138 (37%) (30 excellent, 21 good)	19/51 (37%)	5/51 (10%)	-
Implants Determined to be Failures	18/45 (40%)	7/45 (16%)	73/138 (53%); 2 due to loosening	22/51 (43%)	6/51 (12%)	20 of the 73 implants determined to be failures were removed in 10 patients; (15 replaced with silicone spacers, 4 reinserted with bone cement, and 1 new pyrocarbon implant was inserted). See below for time of removal.
Implants for which an Outcome was Indeterminate	3/45 (7%)	2/45 (4%)	14/138 (10%)	4/51 (8%)	2/51 (4%)	-

\* Note: Success/Failure/Indeterminate criteria were retrospectively defined.

\*\* Note: In the Longer Term Outcome Analysis, any implant removal after device implantation is considered a failure.

**Summary of Long-Term Outcome Analysis:**

Thirty (30) implant outcomes were considered excellent with average last follow-up 7.6 years (range 1.0 - 15.9). Twenty-three (23) of those 30 implants had last follow-up >2 years. Seven (7) of those 30 implants had last follow-up < 2 years. Twenty-one (21) implant outcomes were considered good with average last follow-up 6.8 years (range 1.3 - 16.8). Eleven (11) of those 21 implants had last follow-up > 2 years. Ten (10) of those 21 implants had last follow-up < 2 years. Thus, 34 (67%) of the 51 successful implants had last follow-up greater than 2 years and 17 of the 51 successful implants had last follow-up less than 2 years.

The sponsor stated that on an intent to treat basis when all implanted devices are considered in determining success, 37% (51/138) of the implants had an Excellent or Good outcome and thus were considered successful when applying the more rigorous effectiveness criteria. When only implants with a known outcome are considered (i.e., excluding implants with indeterminate outcome), 41% (51/124) of the implants were considered successful.

Under the modified criteria, successful implants were in 23 (51%) of the 45 RA/SLE patients, and of these patients, 17 (74%) had all their implants considered successful. Therefore, 38% (17/45) of the patients in the RA/SLE cohort had all their implants considered successful when applying longitudinal effectiveness criteria.

For implants demonstrating Excellent and Good outcomes, the primary treatment objectives for all implants were obtained. There were no reports of implanted joint pain at an average follow-up of 7.0 years (range 1.0 to 16.8 years), and no reports of hand or finger pain. The average extension increase was 33.7 degrees (range of -50 to 125 degrees) at an average follow-up of 3.3 years (range 0.1 to 16.8 years). All patients

with a primary treatment expectation of increasing extension showed an extension increase. Five implants in 4 patients with a treatment expectation of joint reduction and/or surface replacement and/or pain relief showed an extension decrease, but had good to excellent post-operative range of motion (ROM) averaging 28.0 degrees (range 20 to 40 degrees). Of the 51 implants considered successful, radiographic data showed 43 (84%) implants reduced and 8 implants subluxed at an average follow-up of 4.2 years (range 0.1 to 13.1 years). No successful implants were dislocated in the long-term.

For the group of 73 implants with an unsatisfactory outcome in 25 patients, 20 implants in 10 patients were removed. Two implants were removed due to loosening (patient #40 at 1.5 years and patient #33 at 4.9 years). The 18 other implants removed were revised due to disease related soft tissue degradation that resulted in flexion contracture (8 implants: 2 in patient #49, 2 in patient #37, and 4 in patient #23), ulnar deviation deformity and dislocation (3 implants in patient #26), or subluxation/dislocation (7 implants: 1 in patient #15, and 2 each in #8, #13, and #39). All removed implants were successfully revised; 15 were replaced with silicone spacers, 4 pyrocarbon implants were reinserted with bone cement, and 1 new pyrocarbon implant was inserted.

The other 53 implants with and unsatisfactory outcome in 18 patients were unsuccessful due to extension contracture or flexion lag (13 implants: 1 each in patients #9, #12, #26, and #39, 2 in patient #28, 3 in patient #12 and 4 in patient #30), lack of extension improvement or extension deficit (27 implants: 4 each in patients #24, #30, #35, and #42, 3 in #50, 2 each in #39, #44 and #51, and 1 each in #8 and #10), recurrent severe ulnar deformity (4 in patient #25), dislocation (7 implants: 4 in patient #28, 2 in patient #32 and 1 in patient #42), and loss of motion (2 implants in patient #4). Thus, of the 73 implants with unsatisfactory outcomes in 25 patients, only 2 were directly related to implant loosening. All other unsatisfactory outcomes were due to disease related soft tissue degradation leading to reduction or loss of motion, joint dislocation, or recurrent ulnar deformity.

#### Comparison of RA/SLE Effectiveness Results

The impact of applying the longer term ("modified") effectiveness criteria to determine treatment outcomes for the RA/SLE patient cohort is shown below. When reductions in treatment improvements at follow-up times of greater than five (5) years are considered, the number of successful implants (excellent and good outcomes) decreases from 82 to 51 (59% to 37%), while the number of implants with unsatisfactory outcome increases by 36 from 37 to 73. For the 36 additional implants with unsatisfactory outcome, 6 implants were removed from 2 patients (4 from patient #23 at 5.4 years due to flexion contracture and ulnar deviation deformity, and 2 from patient #8 at 11.0 years due to subluxation/dislocation); all 6 removed implants were successfully replaced with a silicone spacer. The other 30 additional implants with unsatisfactory outcome were considered failures due to extension lag (15 implants in 6 patients), flexion lag/stiffness (9 implants in 5 patients), dislocation (4 implants in 1 patient), and loss of motion (2 implants in 1 patient). Thus, all 36 additional implants with unsatisfactory outcome under the modified effectiveness criteria were unsuccessful due to disease related soft tissue degradation and attenuation leading to reduction or loss of motion, joint dislocation, or recurrent ulnar deformity.

RA/SLE 1 to 5-Year and Longer Term Outcome Result Comparison*	1 to 5-Year Outcome**		Longer Term Outcome*** (Range of last follow-up time point for patients determined to be successes 1.0 to 16.8 years)	
Number of Implants	138	100%	138	100%
Excellent & Good	82 (46 Excellent & 36 Good)	59%	51 (30 Excellent & 21 Good)	37%
Unsatisfactory	37	27%	73	53%
Indeterminate	19	14%	14	10%

\* Note: Success/Failure/Indeterminate criteria were retrospectively defined.

\*\* Note: In the 1-5 Year Outcome Analysis, a patient may have an implant removal 5 years or more after device implantation and still be considered a success.

\*\*\* Note: In the Longer Term Outcome Analysis, any implant removal after device implantation is considered a failure.

**Implant Safety Criteria for the RA/SLE Case Series:**

The frequency and severity of the following events were evaluated for purposes of determining device safety.

1. Intraoperative implant fracture
2. Non-intraoperative implant fracture
3. Unstable intraoperative bone fracture
4. Post operative bone fractures
5. Implant related infection
6. Adverse biological reaction to implant

**RA/SLE Safety Results**

Safety Issue	Number	Outcome
Intraoperative Implant Fracture During Implantation	2 implants in 2 patients	One had fractured implant removed and new pyrocarbon implant inserted; Other had fractured fragment left in situ and silicone spacer was inserted
Intraoperative Implant Fracture During Revision	6 implants in 3 patients	5 implants in 2 patients revised with silicone spacers; 1 implant in 1 patient had the tip break so the component was implanted with bone cement
No other safety issues*		

\* The sponsor reported no other safety issues for the RA/SLE patients in Amendment 3. However, what the sponsor means is that there were no other reported occurrences of the implant safety criteria listed above. In fact, there were many other adverse events for the OA/Trauma and RA/SLE patients. These events were described in the Original PMA and are summarized later in this review memo.

**Overall Summary (Amendments 3 and 5)**

The sponsor provided information in the PMA regarding Overall Outcomes by combining the treatment outcome results for the OA/Trauma and RA/SLE patient cohorts. However, the sponsor has not provided evidence that these patient groups are poolable; that is, that they are comparable patient populations. On the contrary, the sponsor has provided evidence that these are distinct patient populations. Therefore, the overall summary information that the sponsor included in Amendments 3 and 5 will not be included in this review memo.

**ADVERSE EVENTS REPORTED IN THE CASE SERIES ANALYSIS (AMENDMENTS 3 AND 5) AND IN THE ORIGINAL PMA: (THIS INFORMATION WILL ALSO BE FOCUSED ON BY FDA AT THE PANEL MEETING.)**

The following list contains a summary of adverse events for the 53 patient case series.

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**Panel Please Note:**

**There will be panel questions regarding overall device safety and the following specific adverse events: device removal, post-implantation soft-tissue reconstruction, intraoperative fracture of the device, black staining of tissue, and synovitis**

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<b>Implant Removal</b>	<b>All Diagnoses (n=53)</b>	<b>OA/Trauma (n=8)</b>	<b>RA/SLE (n=45)</b>
• Number of Implants	147	9	138
• Number of Removals	21/147 (14%) (from 12 hands)	1/9 (11%)	20/138 (14%)
• Fracture	0	0	0
• Loosening, Subsidence, Migration	3/147 (2%)	1/9 (11%)	2/138 (1%)
• Clinical Complication	0	0	0
• Disease Progression	18/147 (12%)	0	18/138 (13%)
• All implants were successfully revised; 15 with silicone, 4 primary reinserted with bone cement; and 2 new pyrolytic carbon implants.			
<b>Recurrent Deformity:</b>		62 events affecting 49 implants in 20 patients were reported. 36 events occurred in the first 3 months.	
<b>Implant Fracture (Intra-Operative):</b> Note 1 below		<b>Implants (N=10)</b>	<b>Patients (N=7)</b>
• Fractures during implantation		4	4
• Fractures during removal		6	3
• Additional pyrocarbon implant fractures: The sponsor emphasized that of the 147 primary uncemented ball-and-cup pyrocarbon implants, there were no reports of in vivo implant fracture. However, of the 4 additional pyrocarbon implants (2 condylar design and 2 revision) there were 3 in situ device fractures. These are described in detail in Note 2 below.			
<b>Implant Loosening</b>	8 events for 7 primary case series implants in 5 patients. Only 4 were revised (3 for loosening, revised with cement; 1 for subluxation, revised with silicone spacer)		
<b>Soft Tissue Reconstruction: Post-Device Implantation</b>	11 events 22 (15%) joints in 11 (21%) patients. All but one of the soft tissue reconstruction procedures involved patients in the RA/SLE diagnostic category. 16 of the 22 joints were operated on less than 1 year post-implantation. 3 of the affected joints were eventually removed due to subluxation/dislocation; (2 in 4 days, 1 in 9 years). No patient required multiple soft tissue reconstruction procedures of the MCP.		
<b>Subluxation/Dislocation</b>	35 events affecting 31/147 (21%) implants in 17 primary case series patients.		
	13/35 events in the first 3 months. No action was taken for 2; splint adjustments were made for 3; open reduction was performed on 3; and 5 implants were revised (3 to silicone, 1 with cement, and 1 to a new pyrocarbon). Only one subsequent subluxation/dislocation was reported for these implants; this second event was reported 10 years later.	22/35 events occurred after the first 3 months. 16/22 events occurred in 4 patients at more than 50 months post-implantation. No action was taken for 15 of these events, a soft tissue reconstruction was performed on 1, and 4 were revised to a silicone spacer.	

<b>Histopathology:</b>	<p>Tissue sections from a total of 9 MCP joints with study implants were examined. Histopathologic features observed were consistent with diagnoses of RA and OA. No indications of negative tissue reaction due to the presence of the pyrolytic carbon implants were seen e.g., no foreign body granuloma or other negative foreign body reactions were observed. Carbon particles were observed in 2 patients (pat. #43 and #39).</p> <p>Patient 43 was a Trauma patient who had an intraoperative device fracture during primary implantation. The fragments were removed by drilling. Tissue sample was taken 1.1 years later when device was found to be loose. Histopathologic examination of the subcutaneous tissue stained with carbonaceous debris was performed. The histopathologist reported that there were no inflammatory cells and no cellular reaction to the carbon particles. He concluded by stating that the tissue sections showed proliferative synovitis but it was not a reaction to the carbon particles.</p> <p>Patient 39 was a RA patient who had a dislocation and subluxation event in the right long finger. Tissue samples were taken at 10.5 months post-implantation. The pathologist noted the presence of fine particulate matter. However, he was unable to determine if the matter was within histiocytes or simply within the interstitium. The sponsor concluded that consistent with the results reported in the PMA, there was no evidence of a biological reaction to the particulate matter.</p>
<b>Synovitis:</b>	<p>24 synovitis events were reported in 10 patients affecting 24 implants. Of the 24 affected implants, histopathology tissue samples were available for review on 4. No reaction to the implant was observed for any of the tissue samples.</p>
<b>Black Stain Tissue:</b>	<p>A total of 7 implants caused black stained tissue in 4 patients.</p> <p>Four (4) events occurred during removal of implants from each finger on one patient's hand. All four fractured implants were removed by drilling them out of the bone. After the drilling process, black stained tissue was observed in each finger. No tissue samples were taken from this patient.</p> <p>In addition, there were 3 events observed during operations to remove implants that were potentially loose in 3 patients. Tissue samples from these three patients were excised during removal for histopathologic examination. The sponsor's histopathology summary stated that examination of the tissue did not reveal any negative tissue reaction and all implants were revised (2 to silicone and 1 with cement).</p>
<b>Foreign Body Reactions:</b>	<p>1 report of a foreign body reaction when an implant was revised to a silicone spacer. A histopathologic specimen excised during the reoperation was re-examined and fine particulate matter was found. The histopathologist reported no evidence of biological reaction to the particulate matter.</p>
<b>Subsidence</b>	<p>10 events for 9 primary study implants in 6 patients. Only one of these implants was revised and the reason for revision was loosening (revised with cement).</p>
<p><b>Bone Response – Radiographic Changes</b></p> <ul style="list-style-type: none"> <li>• Lucency</li> <li>• Sclerosis</li> <li>• Heterotopic Bone</li> <li>• Bone Cyst</li> <li>• Bone Erosion</li> </ul>	<p>9 reports of radiographic changes in 6 patients.</p> <ul style="list-style-type: none"> <li>• 5 lucency events were reported for 4 primary study implants in 3 patients; 1 implant was removed and reinserted with cement. No action was taken for the other events.</li> <li>• 1 sclerosis event, no action taken.</li> <li>• 2 heterotopic bone events, no action taken.</li> <li>• 1 bone cyst event, no action taken.</li> <li>• 1 bone erosion event (p.38 of Amendment 3)</li> </ul>

<b>Stiffness/ Loss of Motion</b>	12 events affecting 12 implants in 6 patients. 5/12 occurred at >120mo. 2 were revised with cement due to loosening and soft tissue reconstruction was conducted on 1 implant.				
<b>Bone Fracture</b>	3 events in 2 patients during device insertion and removal				
<b>Sensory Abnormality:</b>	1 patient reported numbness on 2 different fingers beginning 9 years post-implantation. No action was taken, and no further reports of numbness were noted. Another patient reported burning sensation at 9 months post-implantation; MCP motion was satisfactory. No action was taken; no further reports of burning were noted.				
<b>Implant Modification:</b>	5 implant modification events affecting 5 implants in 3 patients. The proximal component stem for these implants was shortened with a rongeur at the time of surgery. These devices were modified to prevent interference with prostheses used in prior total wrist arthroplasty procedures. All of these implants were subsequently removed due to RA/SLE disease progression. The current labeling warns against such implant modifications.				
<b>Excessive Erythema:</b>	2 reports of excessive erythema events in 2 patients. Both events occurred within 8 days of primary implantation surgery. Both were resolved.				
<b>Infection</b>	No reports of implant site infection but 2 superficial wound infections noted after the primary implants were removed. Both infections resolved.				
<b>Implant Specific Pain:</b>	14 reports affecting 13 (9%) primary study implants in 11 (21%) patients. 3 reports due to the procedure; 2 reports of pain in one implant that was revised due to loosening; there was long term chronic pain associated with progressive arthritis in 5 patients (6 implants)				
<b>Window, Months</b>	<b>Patients Followed, N</b>	<b>Patients with Pain Information, N</b>	<b>Patients with Absence of Pain, N (%)</b>	<b>Patients Reporting Implanted Joint Pain, N (%)</b>	<b>Patients Without Pain Information</b>
< 3	53	31	16/31 (52%)	3/31 (10%)	22
3-9	52	13	7/13 (54%)	2/13 (15%)	39
9-18	50	17	9/17 (53%)	2/17 (12%)	33
18-60	41	11	4/11 (36%)	5/11 (45%)	30
60-120	38	11	2/11 (18%)	1/11 (9%)	27
> 120	29	26	15/26 (58%)	0/26 (0%)	3

Note 1: During implantation, after first insertion, sometimes a particular size implant used was too large and would need to be removed. During revision, components generally were well fixed and considerable effort was required to effect removal, often including drilling. For all intra-operative fracture events, either a new pyrolytic carbon implant (2) or a silicone spacer was successfully inserted.

Note 2: The sponsor emphasized that there were no fractures in the 147 primary ball and cup design implants. There were, however, a total of 3 in situ fractures in non-study implants. These were as follows:

- The first fracture occurred 9 years post-op in one of the condylar implants while the patient was lifting a heavy suitcase. The fracture extended transverse through the distal component of the stem. The fractured implant was successfully revised to a metal on plastic implant that was fixed with bone cement;
- The second fracture was also to a condylar implant. This fracture was through the cup of the distal component. The fractured implant was never revised, therefore, a detailed failure analysis could not be conducted; and
- The third fracture occurred through the cup on the distal component of a revision pyrocarbon implant. The primary implant was revised at 1 year due to loosening and a new pyrocarbon implant replaced it. Four years after the first revision, the revision pyrocarbon implant was revised due to loosening to a silicone spacer. During this second revision procedure, a

fracture was identified on the cup of the distal component. The fractured implant was never retrieved, therefore a detailed failure analysis could not be conducted.

The sponsor emphasized that 2 of the 3 fractures were of the condylar design. The sponsor provided a picture of the condylar design on page 67 of Volume 1 of 13 in the Original PMA. The condylar design has a conical shaped bump in the center of the articulating surface of the distal component that interfaces with a groove on the proximal component.

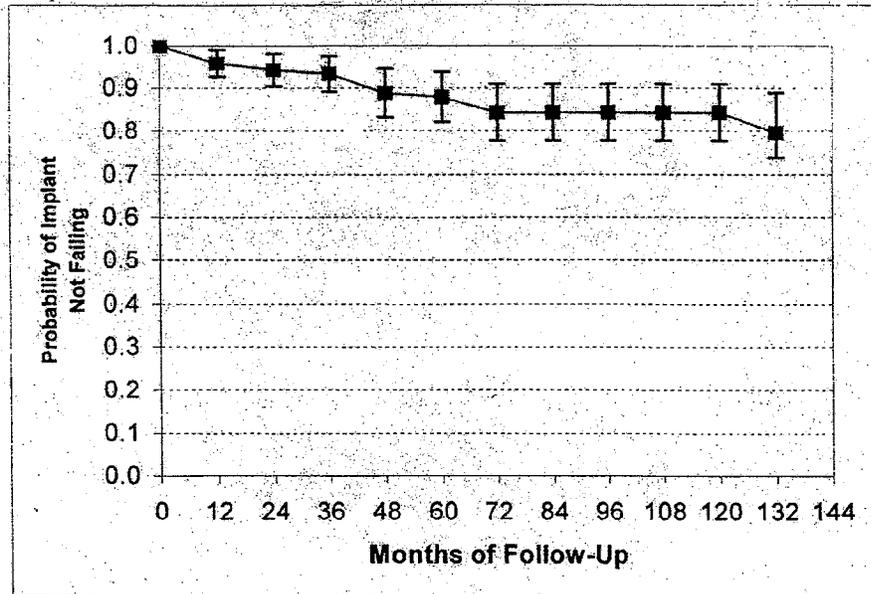
#### **SUMMARY OF SPONSOR'S ORIGINAL PMA CLINICAL DATA ANALYSIS:**

In the Original PMA, all information, clinical findings, and observations recorded in the source documents related to the patients' wrists, hands, fingers and MCP joints at baseline and at all follow-up visits were extracted and entered into the patient database. The patient database included demographic information (age, gender), diagnosis, hand dominance, general medical history, prior treatments, and all available follow-up data on objective clinical variables (MCP joint range of motion (flexion and extension), grip and pinch strength, and ulnar deviation) and subjective clinical attributes (pain, activity level, satisfaction, and cosmesis), radiographic information, surgical information, and all potential adverse events and complications. Kaplan-Meier survival curves for the pyrocarbon MCP implants were provided, discussed, compared to the only survival curve found for MCP silastic spacers in the literature (Hansraj, 1997), and a claim on non-inferiority was made. The demographic data, subjective attributes and objective variables at baseline and follow-up were analyzed and displayed in various tabular and graphical formats. For each subjective and objective endpoint, the sponsor presented descriptive statistics for the study population and a "subgroup" of the control articles and claimed "equivalence" without statistical justification. Potential adverse events and complications related to device safety were identified and analyzed by diagnosis, operated and non-operated joint, finger, and hand.

## Effectiveness Criteria:

## Primary:

- A. Implant Survival with failure defined as:
- Removal for any reason (includes implants removed and replaced with another pyrolytic carbon implant or other device, or removed and reinserted)
  - Implant fracture without removal

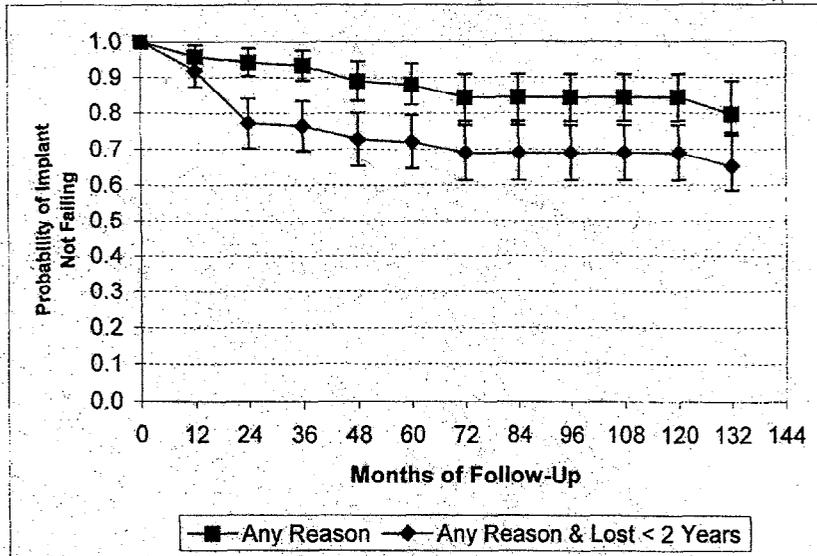


**Figure 9.1-1. Pyrolytic Carbon Implant Survival Curve – Fracture or Removal for Any Reason – Study Population**

Reference Appendices B. 6.2 and Figure 1

At 24 months – 94%; 60 months – 88%; annualized failure rate of 3% per year for the 1<sup>st</sup> 5 years and 1% per year thereafter. Sponsor stated that no baseline factors (e.g., surgeon, age, gender, diagnosis, etc) contributed significantly to implant failure and none were found.

- B. (Worst Case Scenario) Implant Survival with failure defined as:
- Removal for any reason (see above); or
  - Lost to follow-up within two years of primary implant surgery

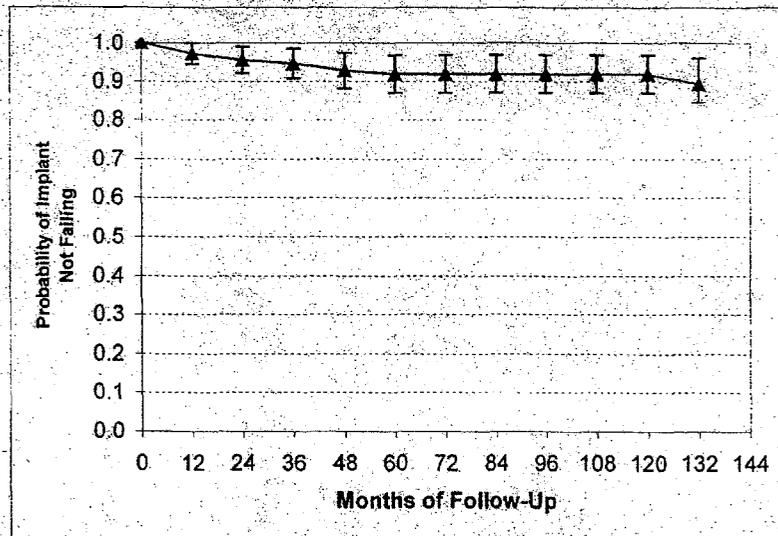


**Figure 9.1-4 Pyrolytic Carbon Implant Survival Curve – Lost to Follow-Up Less Than 2 Years – Study Population**

Reference Appendices B.6.1.1, B.6.1.2 and Figures 1 and 2

At 24 months – 77%.

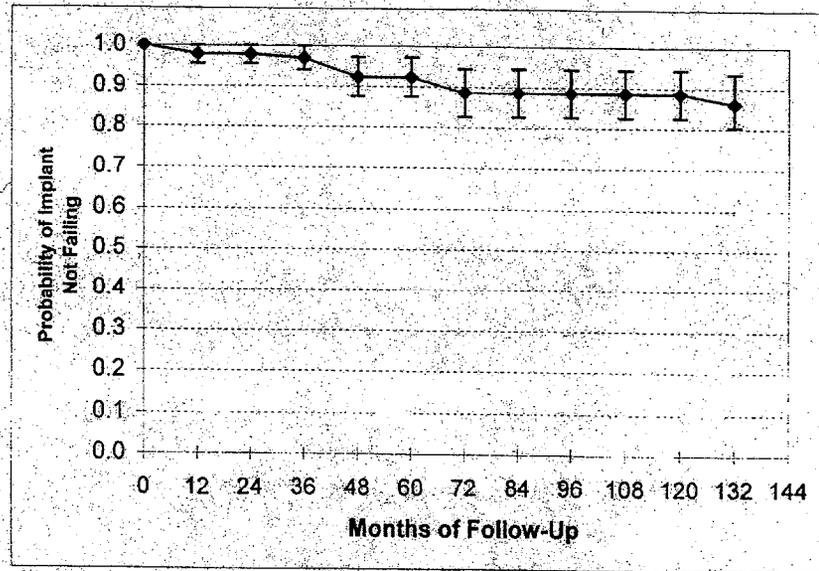
- C. Implant Survival with failure defined as:
- Removal due to an implant related event (implant fracture, loosening, subsidence, migration, dislocation, subluxation, locking or catching of the implant)



**Figure 9.1-2. Pyrolytic Carbon Implant Survival Curve – Implant Related Failure – Study Population**

Reference Appendices B.6.1.3 and Figure 3

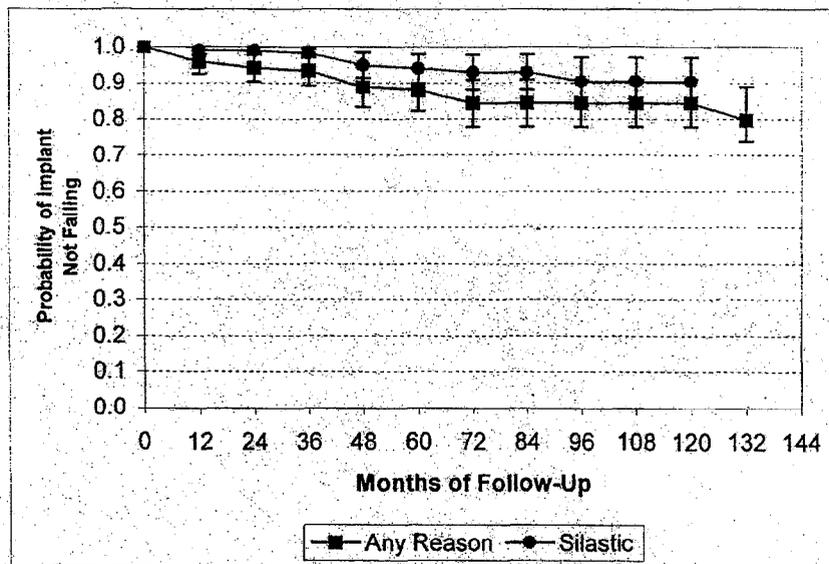
- D. Implant Survival with failure defined as:
- Removal due to a soft tissue related event (limited range of motion, stiffness, recurrent deformity (ulnar or radial deviation, supination flexion deformity, swan-neck deformity of PIP, hyperextension of MCP), or flexion with contraction)



**Figure 9.1-3. Pyrolytic Carbon Implant Survival Curve – Soft Tissue Related Failure – Study Population**

Reference: Appendices B.6.1.4 and Figure 4

Study Compared to Control – Survival Curve:



**Figure 9.1-5. Implant Survival Curves – Removal for Any Reason – Study Population and CP (Hansraj, 1997).**

Reference Appendices B.6.1.2, B.6.3 and Figures 1 and 5.

The sponsor stated that for the control population survival curve does not account for implants that fail within the first 2 years; thus, the curve is artificially elevated for the first 2 years. After this time point, the sponsor stated that the curves track very closely e.g., both curves exhibit an annualized failure rate of approximately 1% between 5-10 years.

In my reading of the Hansraj article, revision (removal) was the reason for decreases in the life table. There were 11 revisions. Please note that there were 12 fractures of which 11 were revised. The sponsor stated that since fracture was not considered a failure that the Hansraj survival curve was artificially inflated. In light of the fact that only one device which fractured was not revised, I believe this is a minor point. The sponsor also stated that Hansraj did not take into account failures that occurred in the first 2 years. However, from my reading of the article, it appears as if there were 3 failures in the first year; all of which were accounted for.

The sponsor presented the following information for the case series patients regarding subjective and objective endpoints and radiographic data:

#### Subjective Measures

- Pain

The sponsor stated that pain relief is hard to localize to the implanted RA joint due to disease throughout the hand, wrist and upper extremity.

Pain Free	Baseline = 11% (4/35)	Last Observation = 49% (21/43)
Over Time	3;3-9;9-18;18-60;60-120;>120mo	16/31;7/13;9/17;4/11;2/11;15/26

- Cosmesis

Acceptable Cosmesis		Last Observation = 88% (14/16)
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- Patient Activity Level

Activity Level – Not Limited	Baseline = 6% (1/18)	Last Observation = 29% (12/41)
Over Time	3;3-9;9-18;18-60;60-120;>120mo	1/18;1/4;1/5;3/12;2/6;1/9;8/25

- Patient Satisfaction

Patient Satisfaction		Last Observation = 79% (38/48)
Over Time	3;3-9;9-18;18-60;60-120;>120mo	25/29;18/21;17/22;8/13;5/9;15/19

**Objective Measures:**

- Pinch Strength

The sponsor stated that grip and pinch strength measurements were measured by certified hand therapists at Mayo Clinic according to general procedures recommended by the American Society of Hand Therapists. Standard equipment such as the Jamar dynamometer, a five-position hand dynamometer, or the NK Digit-Grip device, and B&L Pinch meter are used by the Mayo Clinic. The sponsor stated that traditional dynamometer and pinch gauges have been shown to be reliable test instruments and provided literature support. When strength measurements are conducted according to standard procedures, high inter-rater and test retest reliability can be achieved.

- Appositional Pinch Strength

Pinch Strength –Left Mean (S.D.)	Baseline = 3.72kg (3.35kg) (n=36) Range (0.5-13kg)	Last Observation = 2.83kg (2.02kg) (n=21) Range (0.2 to 6kg)	Mean Change = -1.96kg (3.68kg) (n=15) Range (-10.5 to 3.3kg)
Pinch Strength –Right Mean (S.D.)	Baseline = 4.26kg (5.25kg) (n=37) Range (0-25kg)	Last Observation = 2.57kg (1.87kg) (n=21) Range (0-6 kg)	Mean Change = -1.76kg (5.02kg) (n=17) Range (-19 to 2.5kg)

- Oppositional Pinch Strength

Pinch Strength –Left Mean (S.D.)	Baseline = 2.12kg (2.01kg) (n=35) Range (0-9kg)	Last Observation = 1.86kg (1.80kg) (n=19) Range (0-5.5kg)	Mean Change = -0.09kg (2.12kg) (n=14) Range (-3.4 to 4.8kg)
Pinch Strength –Right Mean (S.D.)	Baseline = 2.30kg (4.13kg) (n=37) Range (0-25kg)	Last Observation = 1.59kg (1.34kg) (n=21) Range (0-4kg)	Mean Change = -0.13kg (1.84kg) (n=16) Range (-3.3 to 4kg)

- Grip Strength

Grip Strength –Left Mean (S.D.)	Baseline = 10.23kg (15.51kg) (n=42) Range (0-80kg)	Last Observation = 8.97kg (11.40kg) (n=27) Range (0.5-54kg)	Mean Change = -4.05kg (13.13kg) (n=23) Range (-62 to 5 kg)
Grip Strength –Right Mean (S.D.)	Baseline = 8.92kg (10.84kg) (n=42) Range (0-65kg)	Last Observation = 9.47kg (13.20kg) (n=28) Range (0-65kg)	Mean Change = -3.62kg (8.87kg) (n=24) Range (-62 to 5)

- Clinical Ulnar Deviation

Ulnar Deviation: Mean (S.D.)	Baseline = 24.27° (20.75°) (n=55) Range (0-85°)	PostOp = 6.71° (8.32°) (n=38; <3mo)	Last Follow-Up = 11.57° (11.29°) (n=67; 12.5mo (1-131mo)) Range (0-35°)
Change from Baseline Mean (S.D.)		PostOp = -12.61° (16.71°) (n=23)	Last Follow-Up = -11.25° (22.96°) (n=32) Range (-85 to -17°)

- Extension Deficit

Extension Deficit: Mean (S.D.)	Baseline = -47.06° (26.44°) (n=141) Range (-130 to 10°)	PostOp = -17.78° (16.63°) (n=136; <3mo)	Last Follow-Up = -20.47° (22.21°) (n=140; 30.90mo (0.56-201mo)) Range (-80 to 25°)
Change from Baseline Mean (S.D.)		PostOp = 28.25° (30.93°) (n=130)	Last Follow-Up = 26.46° (35.04°) (n=134) Range (-60 to 130°)

Significant improvement for RA/SLE patients from baseline to last follow-up but unchanged for OA/Trauma patients.

- Active Flexion

Active Flexion: Mean (S.D.)	Baseline = 81.76° (16.73°) (n=141) Range (30-130°)	PostOp = 56.85° (20.71°) (n=136; <3mo)	Last Follow-Up = 61.71° (23.35°) (n=140; 30.90mo (0.56-201mo)) Range (-5 to 120°)
Change from Baseline Mean (S.D.)		PostOp = -24.55° (26.36°) (n=130)	Last Follow-Up = -20.40° (29.22°) (n=134) Range (-120 to 55°)

Significant change (less flexion) for RA/SLE patients from baseline to last follow-up but unchanged for OA/Trauma patients.

- Arc of Motion

Arc of Motion: Mean (S.D.)	Baseline = 34.70° (24.00°) (n=141) Range (0-95°)	PostOp = 39.07° (16.76°) (n=136; <3mo)	Last Follow-Up = 41.24° (18.71°) (n=134; 30.90mo (0.56-201mo)) Range (0-85°)
Change from Baseline Mean (S.D.)		PostOp = 3.70° (28.57°) (n=130)	Last Follow-Up = 6.05° (31.47°) (n=134) Range (-65 to 60°)

### **Radiographic Information**

#### Patients with Radiographic Information

	Number of Patients w/Radiographs	Number of Implants w/Radiographs
Preoperative	46	124
Early postoperative (<3month)	40	109
Short term follow-up (3mo-1year)	13	34
Long term follow-up (>1yr)	35	97

- Radioulnar angulation of the MCP joint (ulnar deviation)

	PreOp	Early PostOp	Follow-Up >1 year
Implants - N	124	105	87
Ulnar Deviation	19.7+/-14.3°	12.4+/-10.3°	20.4+/-16.8°

- Subsidence of the proximal and distal components

	PreOp	Early PostOp	Follow-Up >1 year
Components - N	218	68	194
Subsidence > 4mm	1/218 (0.4%)	1/68 (1%)	30/194 (15%)

The sponsor stated that no implants were removed for subsidence.

- Position of the MCP joint (reduced, subluxated, dislocated)

	Early PostOp	Short-Term Follow-Up	Long Term Follow-Up
Implants – N	109	34	97
Reduced	103/109 (94%)	29/34 (85%)	69/97 (71%)
Dislocated	3/109 (3%)	3/34 (9%)	14/97 (14%)
Subluxated	3/109 (3%)	2/34 (6%)	14/97 (14%)

Change in periprosthetic bone or implant location:

- Angular Migration

	Early PostOp	Short-Term Follow-Up	Long Term Follow-Up
Components – N	218	68	194
No Angular Migration	213/218 (98%)	66/68 (97%)	176/194 (91%)
Angular Migration	5/218	2/68	18/194: 13 distal, 5 proximal

Sponsor reported that no component was removed for angular migration.

#### **SUMMARY OF MAJOR DEFICIENCIES IDENTIFIED BY FDA IN THE ORIGINAL PMA:**

Analysis of the Original PMA data by FDA resulted in major deficiencies regarding the following issues: (1) appropriateness of the literature controls; (2) failure to define a window of non-inferiority (i.e., delta) with regard to the Kaplan-Meier survival analysis; (3) lack of a statistical comparison to the literature control to support the non-inferiority claim for the Kaplan-Meier survival analysis; and (4) lack of a statistical comparison to the literature control to support the claims of “equivalence” for the subjective and objective endpoints.

#### **SUMMARY OF SPONSOR’S CLINICAL DATA ANALYSIS IN AMENDMENT 2**

The sponsor responded to the major deficiencies identified by FDA in the Original PMA in Amendment 2. The sponsor computed 95% lower confidence-bounds for the primary (implant survival) and “key” secondary effectiveness endpoints for the MCP study population to show that it is unlikely that study results could be inferior to the literature control data. The sponsor computed the probability that the MCP study results for the primary effectiveness endpoint (implant survival) were at least 10% below (delta = 10%) those of the literature control (Hansraj, 1997) at 10 years. This means that the 10-year survival for the study group could be up to 10 percentage points less than the control before it would be considered statistically inferior. This comparison is based, however, not on the observed rates, but the lower limit of the 95% confidence interval. The observed rate for 10-year survival was 84.3% for the pyrocarbon implant and 90.3% for the silastic spacer control (Hansraj, 1997). Assuming variance for the control, the p-value was calculated to be  $p=0.2032$  rather than the traditional  $p=0.05$ . If one uses the more traditional p-value of  $p=0.05$ , the sponsor did not demonstrate that the pyrolytic carbon joint prosthesis was non-inferior to the Swanson Silastic joint spacer with respect to the primary effectiveness endpoint.

For many of the secondary endpoints, the average value for the literature controls was computed, a “clinically acceptable” delta was subtracted to define a lower threshold (a 25% absolute difference was selected for subjective measures like pain, patient satisfaction, and cosmesis and a 10° difference was selected for objective measures like extension lag, active flexion, arc of motion, and ulnar deviation), and the probability that the MCP study results could be below this threshold was computed. The results were broken down by 5-6 time intervals. There were many p-values that were less than  $p=0.05$ , and there were many that were greater than  $p=0.05$ . What stood out in the analysis was that the data were very sparse for the “key” secondary endpoints.

In Table 3 of Amendment 1, the sponsor summarized study population follow-up information for what they identified as “key” secondary effectiveness endpoints. In the column labeled “>18 months,” follow-up rates for these endpoints were as follows: range of motion, 49% (20/41 patients); ulnar deviation, 12% (5/41 patients); joint position (i.e., reduction, subluxation, dislocation), 68% (28/41 patients); strength (pinch or grip), 34% (14/41 patients); patient activity level, 76% (31/41 patients); cosmesis, 22% (5/41 patients); patient satisfaction, 61% (25/41 patients); and pain improvement, 88% (36/41 patients). Please note that for total joint replacement devices, we typically request a minimum of 2 years of follow-up data on each patient before safety and effectiveness are evaluated. Because of the lack of follow-up data for these “key”

secondary effectiveness endpoints, there was little assurance that the data presented is representative of the entire patient population. Therefore, we believe that the subsequent statistical analysis, presented in Amendment 2 and in which they compared the subject and control devices with respect to these secondary endpoints, may have contained patient selection bias.

In addition, rather than defining safety in terms of individual patient and implant success and failure criteria, the sponsor addressed safety only by descriptive statistics (i.e., proportions of each type of intra-operative and post-operative reportable event were compared between the study and control populations). In light of the fact that the patient follow-up rates were low, there was little assurance that the safety data presented is representative of the entire patient population. Therefore, any subsequent statistical analysis in which a comparison is made between the subject and control devices with respect to intra-operative and post-operative reportable events may contain patient selection bias.

**SUMMARY OF MAJOR DEFICIENCIES IDENTIFIED BY FDA IN AMENDMENT 2:**

The sponsor's analysis in Amendment 2 raised the following issues, which were included in a letter from FDA to the sponsor on May 1, 2001:

- FDA believed that the sponsor did not demonstrate that the pyrolytic carbon joint prosthesis was non-inferior to the Swanson Silastic joint prosthesis with respect to the primary effectiveness endpoint;
- In addition, from our review of 20 applicable literature articles the sponsor provided, including the Hansraj article, it appeared as if the researchers evaluated the following effectiveness endpoints in addition to implant survival in their determination of patient and implant success and failure: range of motion, pain, function, strength (grip and pinch), deformity, patient satisfaction, flexion, extension, and radiographic information. We also believe that these types of endpoints including pain, function (finger joint and hand), and radiographic data should be considered primary effectiveness endpoints in addition to implant survival. From our review of the summary information in the patient case histories, it appeared as if there were several patients who were described as in severe pain, unable to grip, had very limited function, or had hands that were "useless" but who did not have the pyrolytic carbon joint prosthesis removed. Although these patients did not have their study implants removed, with the limited amount of information presented for these patients in the case histories, we would not consider these types of outcomes successful. In the sponsor's original PMA submission, they collected and presented this information as secondary effectiveness endpoints. However, rather than defining effectiveness in terms of individual patient and implant success and failure criteria incorporating the primary and secondary effectiveness endpoints, the sponsor compared the study and control means for each secondary endpoint separately. With each secondary endpoint presented and analyzed separately, the amount of information was very sparse. Therefore, FDA believed that the subsequent statistical analysis, presented in Amendment 2 and in which they compared the subject and control devices with respect to these secondary endpoints, may have contained patient selection bias;
- Also, rather than defining safety in terms of individual patient and implant success and failure criteria, the sponsor addressed safety only by descriptive statistics (i.e., proportions of each type of intra-operative and post-operative reportable event were compared between the study and control populations). In light of the fact that the patient follow-up rates were low, we believed there was little assurance that the safety data presented is representative of the entire patient population. Therefore, any subsequent statistical analysis in which a comparison is made between the subject and control devices with respect to intra-operative and post-operative reportable events may contain patient selection bias.

For the above reasons, FDA sent the sponsor the major deficiency letter dated May 1, 2001 (contained in the panel packet). However, we believed that the sponsor might have been able to provide well documented case histories of each patient which might provide a more complete picture of the safety and effectiveness of the Ascension MCP joint prosthesis than what was presented in the PMA up to that point. FDA advised the sponsor that by addressing items in our letter dated May 1, 2001, we were proposing one of potentially several ways in which they might present the clinical data to support the safety and effectiveness of the Ascension MCP joint prosthesis. The sponsor responded to the items listed in our letter dated May 1, 2001 with a reanalysis of the data. The sponsor's reanalysis is contained in Amendments 3 and 5 and was summarized above.

**LITERATURE INFORMATION ON ALTERNATIVE TREATMENTS: INFORMATION CONTAINED IN THE ORIGINAL PMA AND AMENDMENT 3**

The sponsor stated that MCP arthroplasty is most commonly performed using flexible silicone rubber joint replacements. The silicone implants are made to freely move (piston) within the medullary cavity to increase ROM and prolong implant life by reducing the stresses acting in the joint.

Outcomes obtained using the pyrocarbon implants were compared to the historical literature. The historical literature summarized was based on information published for other MCP prostheses and silicone spacers used from 1970 to 1999. A Medline search was performed and data was included if the published study was:

- reported original research and was published no earlier than 1970
- included patients undergoing total joint arthroplasty of one or more MCP joints with a prosthetic implant or silicone spacer
- included at least 10 patients
- had a mean patient follow-up of at least 2 years
- had a minimum follow-up of 100 implant years

A total of 31 peer-reviewed articles met these criteria. Information was extracted and entered into a literature database. Information referred to the aggregate of patients, not data from individual patients.

9 different implant types were represented with the Swanson Silastic spacer being the most common (22/31 articles had data on the Swanson). Gender was reported in 24/31 articles and females comprised 61%-97% of each patient population. Age ranged from 17 years old to 86 years old with a mean age ranging from 40 to 66 years. Diagnosis was reported in 29/31 articles with RA only accounting for 72% of references.

Mean follow up time ranged from 24 months to 138 months, with the mean follow up for this study at 102.6 months. Total person years to follow up ranged from 33 to 2112 person years, with the current study has 450 person years to follow up.

Endpoint	Result:	Comment:
Survival	99% at 24mo; 94% at 60mo; 90% at 120mo	1 article: Hansraj
Removal	Removal: range 0-7%	14 articles Reason for removal: most frequently fracture and infection
Reoperation - Soft tissue reconstruction	Range 0-5%	8 articles
Pain Free	Range: 54%-100% 6 articles	Improvement in Pain Symptoms: 50-82%; 5 articles
Patient Satisfaction	Range: 44%-100%	5 articles
Activity Level Not Limited	Range: 27%, 84%	2 articles: Wilson and Vahvanen
Activity Improvement	Range 52-93%	8 articles
Acceptable Cosmesis	86%	1 article
Improvement in Cosmesis	Range 42-100%	5 articles
Grip Strength	No significant objective measurement demonstrating improvement	1 article: Blair et al., other literature sparse information on grip and pinch strength
Pinch Strength	Post-Op Range: 0 to 6.8kg-force	1 article: Vahvanen
Ulnar Deviation: post-op	Mean Range: 2.8-15° 11 articles	One article showed the deviation range as high as 18°

Extension Deficit:	Pre-Op: Mean Range: -26° to 63° Post-Op: Mean Range: -28° to -6°	Average Follow-Up 59mo. 16 articles
Active Flexion	Pre-Op: Mean Range: Post-Op: Mean Range: 41° to 67°	14 articles
Arc of Motion:	Pre-Op: Mean Range: 17° to 46° Post-Op: Mean Range: 27° to 57°	18 articles
Implant Fracture	Range: 0%-26.2% 21 articles	2 of the articles had an annualized rate of 3%
Implant Subluxation/Dislocation	Range: 0.03% to 27%	8 articles
Implant Subsidence	Range: 0 to 77.8%	4 articles
Infection	Range: 0 to 9.1%	13 articles
Stiffness/Loss of Motion	2 studies: 4.2% and 11%	2 articles: Mannerfelt and Vahvanen
Synovitis	Range 0% to 49%	9 articles

Note: No information on implant loosening, recurrent deformity, sensory abnormality, or bone fracture.