Panel Questions:

1. Device Removal and Post-Implantation Soft Tissue Reconstruction

Summary: Device Removal
A total of 21/147 (14%) implants were removed. Three were removed for loosening and 18 were removed for deformity associated with disease progression related to RA/SLE including extensor lag, flexion contracture, ulnar deviation, subluxation or dislocation. Six (6) implants were removed less than 1 year after implantation; 9 implants were removed between 1 and 5 years after implantation; and 6 implants were removed greater than 5 years after implantation (range 5 – 11 years).

Summary: Post-Implantation Soft Tissue Reconstruction
The sponsor reported that 11 post-implantation soft tissue procedures were performed on a total of 22/147 (15%) joints in 11/53 (21%) patients. All but one of the soft tissue reconstruction procedures involved patients in the RA/SLE diagnostic category. Sixteen of the 22 joints were operated on less than 1 year post-implantation. The sponsor stated that soft tissue procedures are not uncommon because of post-operative disease progression.

1st Question:

What is the impact of the reported device removals and post-implantation soft-tissue reconstructions as they relate to safety and effectiveness of this product? Identify what steps, if any, are necessary to address the risks of device removal and post-implantation soft tissue reconstruction.

2. Intraoperative Fracture of the Device

Summary: Primary Implantation and Revision Fractures
A total of 10 intraoperative fractures occurred in 7 of 53 study patients (13%).

Four (4) of the 10 intraoperative fractures occurred during primary device implantation surgery of 295 components (4/295 = 1.4%). All four events occurred when removing components intraoperatively because the device was too large or additional soft tissue reconstruction was necessary. In 3 of the 4 cases, the fractured component was removed and a new pyrocarbon component was inserted. In the fourth case, the fragment was left *in situ* and a silicone spacer was inserted.

The other 6 fracture events occurred in 3 patients during revision operations of 42 components (6/42 = 14%). The devices fractured during removal. One of the patients had 4 of the 6 fracture events. All four of this patient's devices were revised to silicone spacers. For the other two fracture events, one device was converted to a silicone spacer and the other fractured device (fractured tip of the stem) was reinserted with bone cement.

Summary: Steps the sponsor has taken to address the risk of intraoperative fracture
To address the potential risk of intraoperative fracture for the Ascension MCP device, the sponsor developed instrumentation to aid in component removal (a blunt plastic osteotome called the Ascension Implant Extractor). This instrument was not used in the 53 patient case series. The sponsor also developed and included a section in their Surgical Technique (Amendment 3, Appendix 6, Section 6.15, p.129) on Implant Removal.

2nd Question:

What is the impact of the reported intraoperative fractures as they relate to safety and effectiveness of this product? In addition to developing implant removal instrumentation and revising the surgical technique, identify what steps, if any, are necessary to address the risks of intraoperative fractures.

3. Black Staining of Tissue and Synovitis

Silicone synovitis due to biological response to particulate (wear) debris has been reported in the literature as a potential risk for silicone spacers in the MCP joint and other joints of the hand and wrist. Although the sponsor concluded that there was no adverse tissue reaction to the pyrocarbon MCP joint implant, carbon particles, or "fine particle matter" in samples evaluated by the histopathologist, there were reports of black staining of tissue and synovitis events.

Summary: Black Staining of Tissue
A total of 7 implants caused black stained tissue in 4 of 53 patients (7.5%).

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.

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).

Summary: Synovitis
In addition, a total of 24 synovitis events were reported for 10/53 (19%) patients affecting 24/147 (16%) implants. Histopathology tissue samples were available for review on 5 implants from 2 RA patients and one Trauma patient. From the histopathology report, the sponsor concluded that there was no adverse tissue reaction to the implant, carbon particles, or "fine particle matter" in these samples.

3rd Question:

What is the impact of the reported particulate debris and synovitis as they relate to safety and effectiveness of this product? Based on the sponsor's summary, histopathologist's report, and the black tissue staining and synovitis events discussed in the summary above, identify what steps, if any, are necessary to address the risks of black tissue staining and synovitis.

4. Overall Safety Evaluation of the Device

4th Question:

Based on the retrospective clinical data in the sponsor's case series which included 53 patients and 147 primary uncemented pyrocarbon implants, do the data demonstrate there is reasonable assurance that the probable benefits to health from the use of the Ascension MCP for its intended use and conditions of use, when accompanied by adequate labeling, outweigh any probable risks?

5. Overall Effectiveness Evaluation of the Device

Summary: Device Effectiveness

The sponsor collected retrospective clinical data on 53 patients and 147 primary uncemented pyrocarbon implants. The sponsor retrospectively defined success/failure/indeterminate criteria (outlined on pp.11-12, 15-16 of Amendment 3 and p.6 of Amendment 5) and the results of the sponsor's analysis was as follows:

Case Series Implant Treatment Outcomes:

RA/SLE Implant Treatment Outcomes:*	**1 to 5 Year Outcome**	**Implant Removals: 1 to 5 Year Outcome****	**Longer Term Outcome (Last follow-up time point for patients determined to be successes ranged from 1.0 to 16.8 years)**	**Implant Removals: Longer Term Outcome*****
Number of Implants	138	-	138	-
Successful Implants	82/138 (59%) (48 excellent, 34 good)	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	51/138 (37%) (30 excellent, 21 good)	-
Implants Determined to be Failures	37/138 (27%); 2 due to loosening; see review memo for additional reasons for implant failures	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).	73/138 (53%); 2 due to loosening; see review memo for additional reasons for implant failures	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	19/138 (14%)	-	14/138 (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.

OA/Trauma Implant Treatment Outcomes:*	Outcome (Range of last follow-up time point for patients determined to be successes 3.5 to 17 years)	Comment
Number of Implants	9	-
Successful Implants	7/9 (78%) (6 excellent, 1 good)	-
Implants Determined to be Failures	1/9 (11%)	Failure Due to Loosening: 1/9 at 1.1 years (revised with a new pyrocarbon implant with cement).
Implants for which an Outcome was Indeterminate	1/9 (11%)	-

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

5th Question:

Based on the retrospective clinical data in the sponsor's case series which included 53 patients and 147 primary uncemented pyrocarbon implants and the sponsor's retrospectively defined success/failure criteria and analysis, do the data demonstrate there is a reasonable assurance that in a significant portion of the target population, the use of the Ascension MCP for its intended use and conditions of use, when accompanied by appropriate labeling, will provide clinically significant results? Please consider whether the data support each of the proposed indications for use or a more specific list of indications for use.

6. Patient Labeling (provided in Appendix 5 of Amendment 3)

6th Question:

Please identify what additional information, if any, the sponsor should provide in their patient labeling.