Food and Drug Administration
Center for Devices and Radiological Health

Brief Summary Orthopedics and Rehabilitation Devices
Panel of the Medical Devices Advisory Committee
Meeting
April 20, 2023

Introduction:

On, April 20, 2023, the committee discussed, made recommendations, and voted on the clinical information related to the *De Novo* request for the NUsurface Meniscus Implant sponsored by Active Implants, Inc. The device is a polymeric disc-shaped device implanted in the medial compartment of the knee to distribute load between the distal femur and proximal tibia and is intended to improve pain and function in the medial compartment of a knee in which the medial meniscus has been resected.

Panel Deliberations/FDA Non- Voting Questions

1. Patient Population:
   Based on the modified MERCURY dataset subgroup analysis, the sponsor has identified a target population that includes patients with mild or greater pain, mild to moderate arthritis, and previous meniscectomy, and meeting inclusion/exclusion criteria, specifically the exclusion of patients with meniscal extrusion ≥5mm and tibial spine height <11mm.
   - Please comment on what patient population(s) would benefit from this device, in consideration of available alternative non-surgical and surgical treatments.
   - Please comment on the clinical relevance of the sponsor's modified target population.

Panel Consensus Summary:

The Panel generally believed that the clinical patient population will likely be a relatively small subset relative to the general population, but there was a general consensus that there may be a small subset of patients that would benefit from this device. However, the Panel also had some concerns about the statistical analysis presented and also voiced some concerns regarding the ultimate biomechanical strength and the risk of deterioration of the device that had perhaps not been fully elucidated in the discussions.

2. Clinical Success Criteria and Secondary Surgical Interventions:
   Overall clinical success for the modified MERCURY dataset was defined as improved $KOOS^{overall}$ and $KOOS^{pain}$, positive MRI, and no Automatic Study Failure (ASF). The Statistical Analysis Plan for the modified MERCURY dataset predefined Automatic Study Failures (ASF) as secondary surgical interventions (SSI) to permanently remove the device and revisions to reposition or replace the device. 17% (12/72) of NUsurface subjects experienced a device-related SSI and 25% (3/12) of those subjects had more than one SSI.
   - Please discuss the adequacy of the overall clinical success criteria and the clinical significance of the SSIs related to the device.
   - Please comment on the classification of these SSIs as ASFs.

Panel Consensus Summary:

The Panel generally believed that there was a lack of consensus regarding the adequacy of the overall clinical success criteria specifically regarding comparison beyond two years to other surgical alternatives. Also, the clinical significance of the secondary surgical interventions was felt by the Panel to be appropriately classified as Automatic Study Failures.

3. Sub-group Analysis:
   The sponsor provided a subgroup analysis intended to identify a modified target population with a reduced rate of SSIs from the unmodified MERCURY dataset. The modified MERCURY dataset involves the exclusion of meniscal extrusion ≥5mm and tibial spine height <11mm. Please comment on the overall success rate of the modified MERCURY dataset.

   - Please comment on whether the modified MERCURY dataset provides sufficient information to understand whether the device improves pain and function in the medial compartment of a knee in which the medial meniscus has been resected.
   - Please comment on the study design characteristics as different datasets were utilized compared to a non-surgical control for the MERCURY trial, modified MERCURY dataset, and MCT study.
   - Please comment on the benefit-risk profile for use of the NUsurface Meniscus Implant in alternative subgroups.
   - Are there any additional subgroups in which the NUsurface Meniscus Implant would have a favorable benefit-risk profile?

Panel Consensus Summary:

The Panel generally believed that there were data presented that did show that there was an improvement in pain in the modified MERCURY dataset; however, the Panel raised concerns regarding the criteria of the modified dataset and the extrapolation of those results to a more general population. With respect to the study design characteristics, some members of the Panel felt it was appropriate to use a non-operative control while others thought that a sham surgical control may have been a more beneficial comparator. With respect to the benefit-risk profile for the use of the implant, the Panel was in consensus that the data presented were insufficient to reach a conclusion. And with respect to additional subgroups for which the implant would have a favorable benefit-risk profile, the Panel was also in consensus that the data presented were insufficient to reach a conclusion. Some panel members did note that there may be a small segment of patients for whom this device may be beneficial.

4. Patient Preference Information:
   Patient preference information (PPI) has been provided to support benefit-risk determination.
   - Please comment on the design and execution of the current PPI study (Study 7).
   - Please discuss the contribution of the PPI datasets to the final benefit-risk determination.

Panel Consensus Summary:

The Panel generally believed that the PPI studies had significant methodical issues which limited their applicability for drawing conclusions with respect to the final benefit-risk determination. Specifically, there were concerns regarding the merging of disability and pain and the way in which the questionnaire was presented to respondents. Although one member noted that the sponsor may not have been aware it was necessary, the majority of the Panel had concerns about the lack of IRB approval exemption prior to proceeding with the PPI studies.

5. Risk Mitigation:
   The sponsor has identified several key considerations in risk mitigation, including the appropriate selection of patients (e.g., exclusion of meniscal extrusion >5mm and tibial spine height <11mm) and a more detailed surgical technique (e.g., the ability to precisely identify the appropriate device size and implant the device). The sponsor reported inter-rater disagreements over the meniscal extrusion and tibial spine height exclusion criterion.
   - How might these factors impact the clinical reproducibility, particularly the clinician's ability to identify patients that would benefit from the device?

Panel Consensus Summary:

The Panel generally believed that the inter-rater disagreements for tibial spine height measurements were a significant concern for reproducibility and clinical applicability. The radiology expert on the Panel noted that while meniscal extrusion is a common radiological measurement, tibial spine height is not typically measured. Panel members raised a concern that the tibial spine height measurement will likely need to be performed by surgeons that may not have the same level of expertise as radiologists. Some panel members raised concern whether this measurement could be accurately measured on a coronal magnetic resonance image. Overall, there was concern regarding whether these measurement factors will impact the clinical reproducibility due to the inherent heterogeneity in the measurement itself within the study observations presented.

Panel Voting Question

Based on a consideration of the clinical information provided, do the probable benefits to health of the NUsurface Meniscus Implant outweigh the probable risks when used in patients in accordance with the proposed indications for use?

Panel Summary:

There were 9 voting members, and the panel voted:

- *2 yes*
- *6 no*
- *1 abstain*

Summary of votes:

The majority of the Panel voted "no" citing concerns that the clinical evidence presented did not support a positive benefit-risk profile. They noted that the failure rate was high, particularly given the fact that the clinical trial represented near ideal clinical conditions, with the subgroup subjects representing an ideal patient population and surgeons with NUsurface-specific expertise implanting the device. Another concern was the quality of the clinical evidence presented to the Panel, noting inconsistencies in the success criteria, missing data, difficulties with the subgroup analysis, and concerns about the differences in Automatic Study Failures between the study arms. In general, they did not agree that a change in labeling or indications for use would adequately address their concerns about the data. The Panel members who voted "yes" felt there was sufficient scientific evidence that a narrow population would benefit from the device with regards to improvements in pain and function. Although they felt the benefits outweighed the risks, they recommended consideration of post-market clinical data collection. The Panel member who abstained acknowledged the unmet need for this patient population and stated that, while the benefits may be limited, the risks also did not seem significant; however, ultimately the indications as presented (i.e., including patients with mild pain and function) was considered too broad.

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