

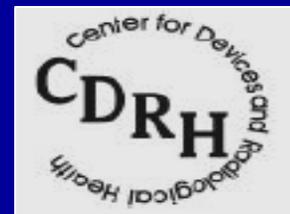
Prestige® Artificial Cervical Disc Post-approval Study Expectations



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Protecting and Promoting Public Health



Outline

- Post-approval Study Principles
- Need for Post-approval Studies
- FDA Postmarket Concerns for Prestige
- Sponsor's Proposed Study Plan
- FDA Assessment
- Panel Questions

Post-approval Study Principles

- Objective is to evaluate device performance and potential device-related problems in a broader population over an extended period of time after pre-market reasonable assurance of safety and effectiveness.
- Post-approval studies should not be used to evaluate unresolved issues from the pre-market phase that are important to the initial determination of reasonable device safety and effectiveness.

Need for Post-Approval Studies

- Address Premarket Data Limitations
- Balance Premarket Data Limitations
- Account For Panel Recommendations
- Gather Essential Postmarket Information

FDA Postmarket Concerns about Prestige

1. Longer-term safety & effectiveness
2. “Real world” performance
3. Effectiveness of training program
4. Sub-group performance
5. Outcomes of concern
 - Metal debris, adjacent segment degeneration, heterotopic ossification

Sponsor's Post-approval Study Plan for Prestige Cervical Disc

Design: Follow-up of non-inferiority trial patients and continued access patients carried out to 7 years

Hypothesis: Success of Prestige group is not lower than control group (anterior cervical fusion) by more than 10%.

Study: Overall success will be assessed using a composite endpoint analysis at 5 and 7 years.

All 4 key safety & effectiveness variables must be met:

1. Postoperative Neck Disability Index score ≥ 15 point increase from preoperative state
2. Maintained or improved neurological status
3. No serious implant/surgical associated adverse events
4. No "failure" surgeries (e.g., revisions, removals, supplemental fixations)
- ~~5. Disc height success~~

Sponsor's Post-approval Study Plan for Prestige Cervical Disc

- **Population:** Premarket study patients (same sites)
No new enrollees.
- **Enrollment:** **Voluntary**, expected minimum of 200 patients (Prestige & ctl) at 7 years; (baseline 276 Prestige, 265 ctls)
- **Data collection:** At **two** time points of **5** and **7 years**
(As of Oct, 2006, pivotal trial subjects should reach the 2-year postoperative date)
- **Annual reports:** To be submitted until the final post-approval study report at the 7-year time point.

Post-approval Study – Assessment of Sponsor’s Plan

FDA Questions & Considerations	Limitations of Sponsor’s Plan
<p data-bbox="195 695 1264 755">1. <u>Long-term safety & effectiveness</u></p> <p data-bbox="262 797 1249 1079">Drop-outs and loss to follow-up remains a concern and the post approval study should be designed with this in mind.</p>	<p data-bbox="1306 695 1864 906">Plan is to follow only a subset of the premarket cohort.</p> <p data-bbox="1306 948 1797 1084">Inadequate study sample size.</p> <p data-bbox="1306 1127 1860 1263">No plan to enhance follow-up.</p>

Loss to Follow-up (LTFU) Rate

To have 100 patients 5 years later for each group (tx or ctl)

LTFU Rate Annual	5%	10%	15%	20%
# needed at 2 year start time	130	170	226	306

Actual LTFU rates in PMA without functional spinal unit height

	Prestige	Control
12-month	4.3%	13.7%
24-month	6.6%	17.6%

Post-approval Study – Assessment of Sponsor’s Plan

FDA Questions & Considerations	Limitations of Sponsor’s Plan
<p>2. <u>Real world performance</u></p> <p>Without new enrollees will the data collected on the subset of subjects be adequate to assure the safety & effectiveness for the broader population that will receive this device after approval?</p> <p>How representative will subjects be?</p> <p>How representative will the physicians be?</p>	<p>Insufficient data.</p>

Post-approval Study – Assessment of Sponsor’s Plan

FDA Questions and Considerations	Limitations of Sponsor’s Plan
<p>3. <u>Effectiveness of training program</u></p> <p>The post-approval study should include an evaluation of training and learning curve. Outcomes may vary by surgical volume.</p>	<p>Not addressed.</p>

Post-approval Study – Assessment of Sponsor’s Plan

FDA Questions and Considerations	Limitations of Sponsor’s Plan
<p>4. <u>Sub-group performance</u></p> <p>How will this device surgery fare for special patient groups?</p> <p>Subgroup analysis is important. (e.g., age, surgical level and indication)</p>	<p>No subgroup analysis is planned. The study population may be very heterogeneous.</p>

Post-approval Study – Assessment of Sponsor’s Plan

FDA Questions and Considerations	Limitations of Sponsor’s Plan
<p>5. <u>Outcome of concern – Metal debris</u> Further study should be conducted on metal debris. New enrollees and a larger cohort seem warranted.</p>	<p>Will continue study of metal debris with 25 patients.</p>
<p><u>Outcome of concern – ASD</u> Are 200 patients sufficient to evaluate? Is 7 years long enough?</p>	<p>Not fully addressed.</p>
<p><u>Outcome of concern – Other</u> Heterotopic ossification and other infrequent adverse events.</p>	<p>Unclear if plan will provide sufficient data.</p>

FDA Postmarket Concerns about Prestige

1. Longer-term safety & effectiveness
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Question #1

Keeping in mind our concerns about long-term performance in a “real world” broader population, please discuss whether the continued follow-up of the premarket cohort will provide sufficient assurance about the long-term safety and effectiveness of Prestige after approval.

Question #2

Please discuss

- The adequacy of the metal debris study
- Concerns about adjacent segment degeneration
- Concerns about other potential infrequent outcomes, such as heterotopic ossification

Thank You!



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