24 Hour Summary of the Circulatory System Devices Panel Meeting
Lutonix 014 DCB
February 17, 2021

Introduction:

The Circulatory System Devices Panel of the Medical Devices Advisory Committee to the Food and Drug Administration met on February 17, 2021 to discuss and make recommendations on the PMA application for the Lutonix 014 Drug Coated Balloon (Lutonix 014 DCB), including whether the device demonstrates a reasonable assurance of safety and effectiveness in treating patients with critical limb ischemia (CLI).

The sponsor has proposed the following Indications for Use:

The Lutonix 014 Drug Coated Balloon PTA catheter is indicated for patients with critical limb ischemia who have obstructive de novo or non-stented restenotic lesions in native popliteal, tibial, and peroneal arteries up to 320 mm in length and 2.0 to 4.0 mm in diameter

Panel Deliberations/FDA Questions:

Question 1: (a) Appropriateness of 6-month endpoint timepoint and (b) acceptability of inclusion of Rutherford Classification 3 (RC3) patients in the clinical study.

a. The panel believed that a 6-month primary effectiveness endpoint was an appropriate assessment timepoint for a CLI trial. However, longer-term treatment durability (12 months and beyond) should also be demonstrated.
b. Panel members expressed concern that some patients enrolled in the Lutonix pivotal trial were not truly representative of the CLI population (e.g., RC3 subjects and patients with primarily short TASC A lesions that are associated with a low amputation risk). The panel concluded that RC 3 patients should not be incorporated in a CLI trial.

Question 2: Clinical meaningfulness of primary effectiveness endpoint results

The panel largely agreed that a 10.5% treatment improvement observed for the Lutonix 014 DCB vs. percutaneous balloon angioplasty (PTA) at 6 months was not clinically significant, particularly because secondary endpoint outcomes showed no additional benefit of the DCB compared to PTA. Some panelists were concerned that the primary endpoint results favored the PTA group starting at 12 months follow-up and continued through 36-months. Additionally, the primary endpoint was driven by the clinically driven target lesion revascularization (CD-TLR),

which was subject to bias given the single-blinded trial design. Many panel members noted that study design and execution limitations presented challenges with interpreting trial results.

Question 3: Effect of missing data on study conclusions

The panel agreed that the large overall amount of missing data and the relatively greater amount of missing data in the PTA group vs. the Lutonix 014 DCB group impacted study outcome interpretation and limited analytical precision. Unknowns related to the reasons for missing data increased levels of uncertainty regarding study conclusions.

Question 4: Subgroups where benefit may be demonstrated

The panel agreed that specific patient populations or vessel characteristics that would particularly benefit from the Lutonix 014 DCB were not identified.

Question 5: Wound healing as support for effectiveness

The lack of a prespecified wound healing assessment protocol, independent review of wound healing assessments, and documentation of healing resulted in uncertainty regarding the wound healing data. Therefore, the panel could not adequately assess the results and did not identify an improvement in wound healing associated with the Lutonix 014 DCB vs. PTA. The panel recommended that future CLI studies should include a standardized wound healing assessment method and an independent wound healing monitor.

Question 6. Additional secondary endpoints as support for device effectiveness: (a) unplanned minor amputation and (b) CD-TLR

a. Given the heterogeneity associated with the patient population and course of treatment and the small number of patients who exhibited amputation, the panel commented that there were not enough data to suggest that the unplanned minor amputation rate supports the effectiveness of the Lutonix 014 device.
b. The panel did not believe that the difference in CD-TLR at 6 months (with no benefit thereafter) provided additional support for the Lutonix 014 DCB effectiveness. One panel member noted that although CD-TLR rate was important, there was little confidence in the data given the study limitations and potential bias.

Question 7. Benefit-Risk Profile

The majority of panel members believed that the totality of the data did not support a positive benefit risk profile because the effectiveness data were limited (not statistically significant, not durable, and may have been affected by bias), and although no safety signals were observed, the amount of safety data (particularly long-term data) is limited. A small number of panel members supported a positive benefit risk profile given the need for new therapies to treat CLI, the benefit of DCBs in other vascular territories, and absence of safety concerns in the Lutonix DCB study data.

Question 8. Post-Approval Study (PAS)
The panel agreed that a post-approval study is only appropriate when there is sufficient evidence of clinical benefit. Additional data with improvements in study execution would be needed prior to considering a PAS. If a PAS were to be considered, remaining questions regarding effectiveness would not be addressed by a small, single-arm study. A PAS would require rigorous, independently-assessed wound healing data.

Vote:

Voting Question 1, regarding whether there is reasonable assurance that the Lutonix 014 DCB is **safe** for use in patients who meet the criteria specified in the proposed indication, the panel voted:

- Yes: 15
- No: 2
- Abstain: 1

Voting Question 2, regarding whether there is reasonable assurance that the Lutonix 014 DCB is **effective** for use in patients who meet the criteria specified in the proposed indication, the panel voted:

- Yes: 2
- No: 15
- Abstain: 1

Voting Question 3, regarding whether **the benefits outweigh the risks** of the Lutonix 014 DCB for the proposed indication, the panel voted

- Yes: 3
- No: 14
- Abstain: 1