Questions for the Advisory Committee Meeting for the Lutonix 014 DCB

1. Protocol Changes and Patient Population

The sponsor has made a number of protocol changes during the course of the pivotal trial, many of which occurred after a substantial number of subjects had enrolled. FDA believes that some of these changes may affect the interpretability of the study results.

a. Rutherford Category 3 (RC3) patients were included in order to increase enrollment. RC3 claudication patients ultimately accounted for 9.5% of enrolled patients. Please discuss the appropriateness for whether RC3 patients should have been included within the study, and whether the study results can be generalized to the CLI patient population given this inclusion.

b. The sponsor shortened the primary effectiveness endpoint timepoint from 12 months to 6 months. Please discuss whether the use of a 6-month timepoint for the primary effectiveness endpoint of above ankle amputation and primary patency (freedom from target lesion occlusion or clinically-driven target lesion revascularization) is appropriate to assess device effectiveness in CLI patients. Please also comment on the importance of evaluating the data at longer term timepoints.

2. Primary Effectiveness Results

The final study protocol incorporated several interim analyses and a modified co-primary effectiveness endpoint (the composite of limb salvage and primary patency) for full flow pathways and proximal segment flow pathways. Limb salvage was defined as freedom from above ankle amputation, and primary patency was defined as freedom from target lesion occlusion or clinically-driven target lesion revascularization. To control the overall type I error rate at 0.025, these protocol changes required a significance level of 0.0085 for superiority hypothesis testing. The primary effectiveness endpoint analysis demonstrated a 10.5% improvement for the DCB arm at 6 months, which did not reach statistical significance (p-value=0.0222).

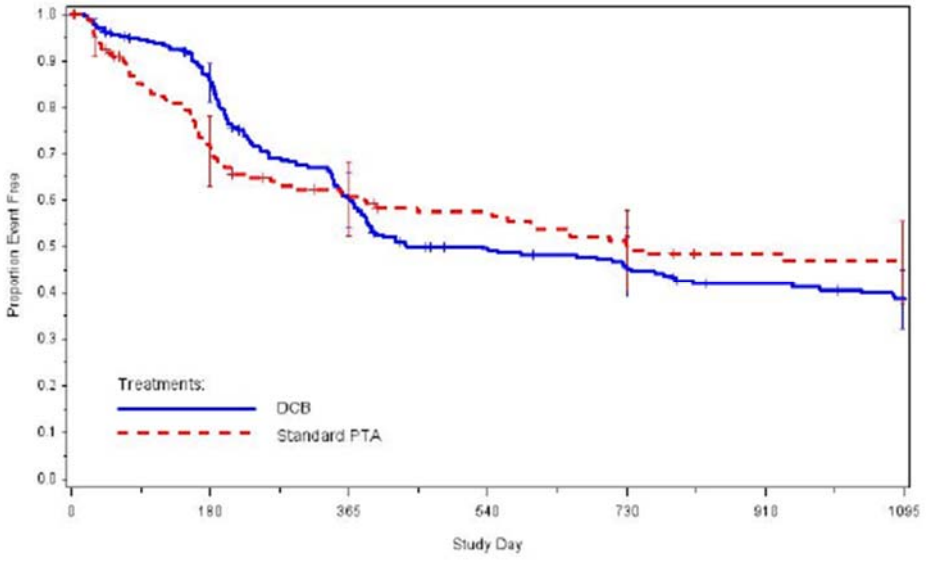
	DCB (N=323) n/N (%) (95% CI)[1]	**PTA (N=184) n/N (%) (95% CI)[1]**	**Difference in Response (95% CI)[2]**	**P-value[3]**
Freedom from Primary Effectiveness Failure at 6 Months	201 / 269 (74.7%) (69.1%, 79.8%)	88 / 137 (64.2%) (55.6%, 72.2%)	10.5% (0.3%,18.8%)	0.0222 **NS**
Composite Endpoint Failure Events Through Day 210, n (%)[4]				
Subjects with major amputation	4 (1.5%)	3 (2.2%)		
Pathways with clinically-driven TLR	28 (10.4%)	30 (21.9%)		

Pathways with primary patency failure	65 (24.2%)	46 (33.6%)		

NS = Non-significant
[1] 95% CI based exact binomial distribution
[2] Based on the model estimated response rates in both groups
[3] One-sided Wald Test based on model estimate of DCB treatment effect and subject as a random effect
[4] Subjects may fail primary effectiveness due to more than one cause and TLR failure is a component of primary patency failure

Further, the primary effectiveness endpoint rate began to numerically favor the PTA group at 12 months and thereafter, with a 5.8% benefit for the PTA arm at 12 months.

	Freedom from Primary Effectiveness Failure		
Visit	**DCB Pathways (N=323) Response Rate**	**PTA Pathways (N=184) Response Rate**	**Difference (95% CI)[1]**
30 Days	283 / 294 (96.3%)	144 / 156 (92.3%)	4.0% (-1.0%, 7.9%)
6 Months	201 / 269 (74.7%)	88 / 137 (64.2%)	10.5% (0.3%, 18.7%)
12 Months	128 / 251 (51.0%)	75 / 132 (56.8%)	-5.8% (-17.0%, 5.2%)
24 Months	84 / 228 (36.8%)	54 / 123 (43.9%)	-7.1% (-17.5%, 4.5%)
36 Months	58 / 210 (27.6%)	29 / 100 (29.0%)	-1.4% (-11.6%, 11.3%)

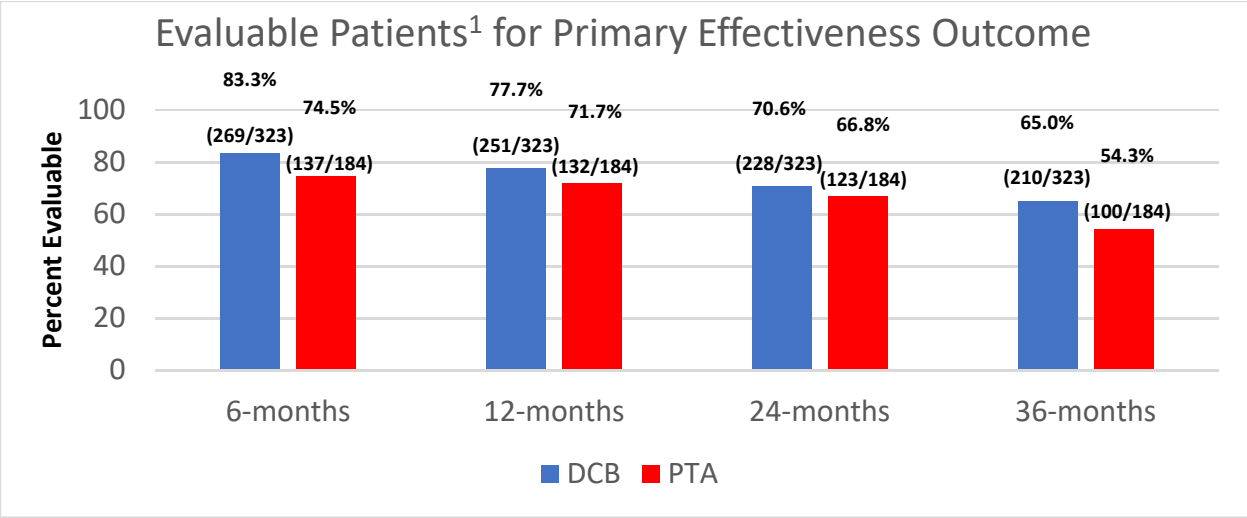


	Flow Pathways Left				
Group	Day 1	Day 180	Day 365	Day 730	Day 1095
DCB	301	235	150	91	59
PTA	163	98	67	55	30

Please discuss the clinical significance of the 10.5% improvement for the DCB arm at 6 months that was no longer present starting at 12 months post-index procedure and continued to favor the PTA arm through 36 months.

3. Missing Data

The was a substantial amount of missing primary effectiveness endpoint data.



[1] Percent evaluable = Randomized Flow Pathways – [(Death) + (LTFU) + Withdrew + Other)]/Randomized Flow Pathways

The rates of missing data for both study arms at each time point were as follows:

- 16.7% for the DCB arm and 25.5% for the PTA arm at 6 months
- 22.3% for the DCB arm and 28.3% for the PTA arm at 12 months
- 29.4% for the DCB arm and 33.2% for the PTA arm at 24 months
- 35.0% for the DCB arm and 45.7% for the PTA arm at 36 months

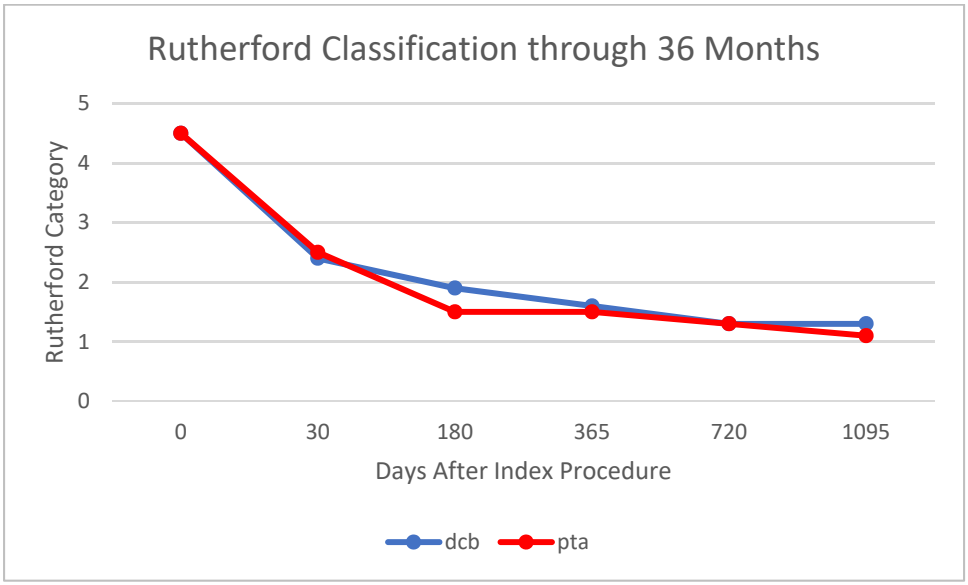
The missing data were due to deaths, lost-to-follow up (LTFU) and withdrawn consent, in which no primary effectiveness outcome could be evaluated. Please discuss the potential impact of missing data (and missing data imbalance between treatment groups) on the interpretation of the study results at 6 months and later follow-up time points.

4. Subgroup Analyses

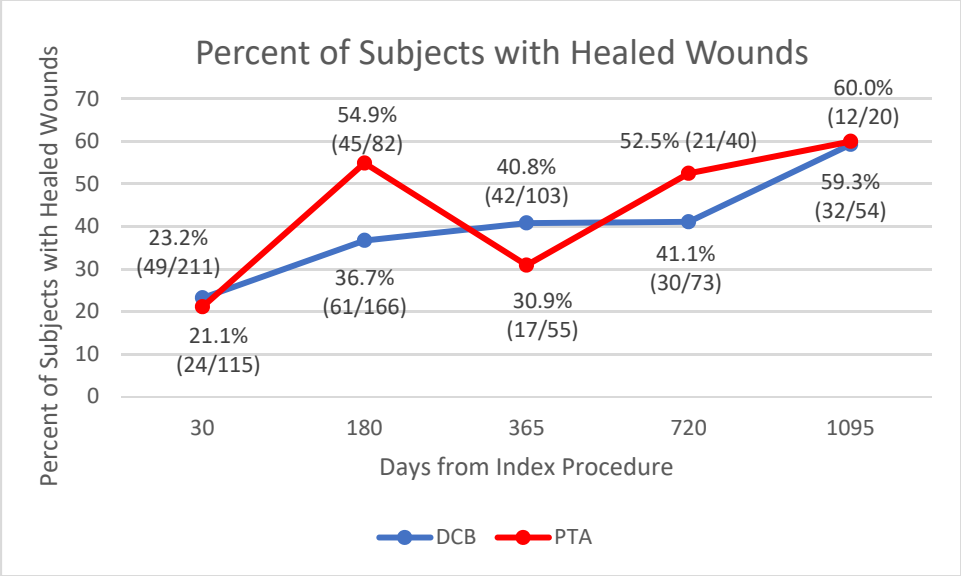
The sponsor included additional effectiveness analyses and conducted various subgroup analyses to help identify specific subsets of patients or lesion characteristics in which the test device might show benefit, including a "proximal segment" analysis, patency excluding "early recoil," and various subgroup analyses. Please discuss whether there are specific patient populations or vessel characteristics that appear to particularly benefit from use of the Lutonix 014 DCB vs PTA.

5. Secondary Endpoint for Wound Healing (including Infectious and Gangrenous Wounds)

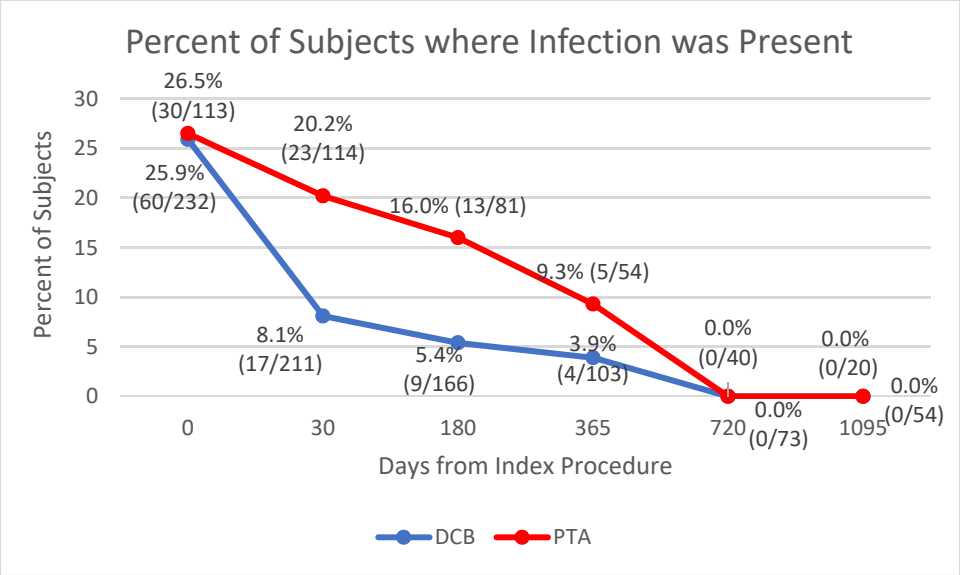
Relief of ischemic pain, mobility, wound healing, and successful infection treatment are important objectives of revascularization procedures in CLI patients. Regarding pain and mobility, in the Lutonix pivotal trial, quality of life measures utilizing the EQ-5D questionnaire and Walking Impairments Questionnaire showed no added benefit of the Lutonix 014 DCB vs. PTA. There was also no evidence of Rutherford Classification improvement associated with the Lutonix 014 DCB vs. PTA.



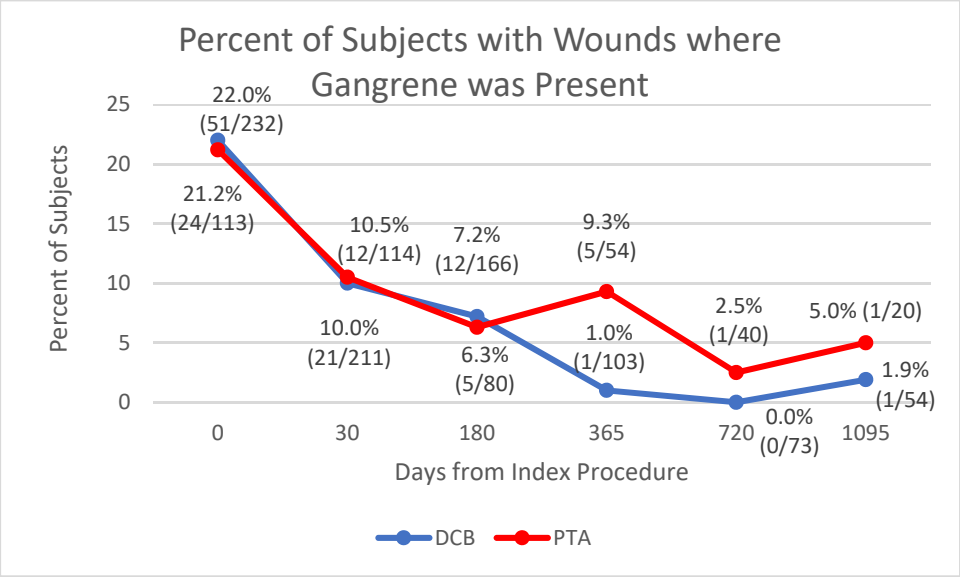
Regarding wound healing, wound assessments were based on each site's wound care program. Wound evaluation and treatment were conducted by unblinded physicians, photographs were not always taken or mandated, and wound data did not undergo third-party independent review. Regarding healed wounds, there was a 18.2% difference in favor of PTA at 180 days but a 9.9% difference in favor of DCB at 365 days. Wound healing then favored PTA by a difference of 11.4% at 720 days, and essentially equal at 1095 days.



For infected wounds, numerical differences in favor of the Lutonix 014 DCB group were observed at 30, 180, and 365 days, though FDA has not been able to draw any clear conclusions from these data given these analyses were limited by small sample sizes and non-rigorous wound assessments.



For gangrenous wounds, a small numerical difference in favor of the Lutonix 014 DCB was observed at 365, 720, and 1095 days.



However, the sample size was small, and limitations of the wound assessment methodology need to be considered. Specifically, wound assessments were performed by physicians

unblinded to treatment group, were limited by incomplete photographic data collection, and did not undergo third-party independent review.

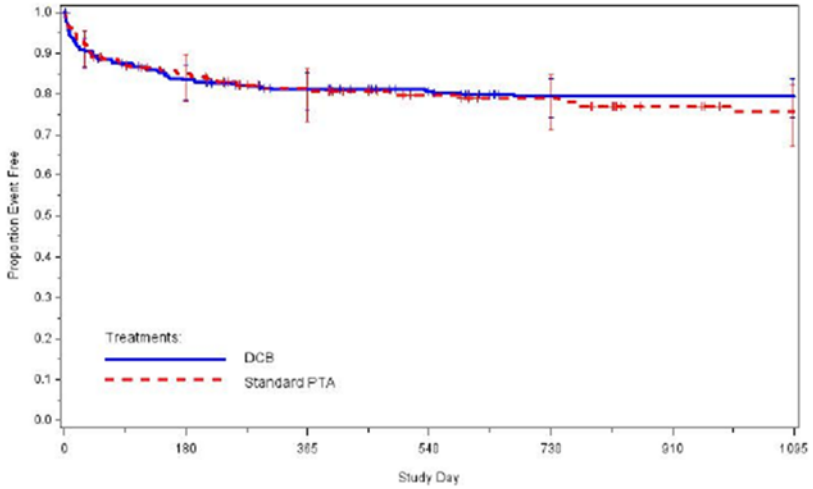
Please discuss if there are any clinically-meaningful improvements in ischemic pain, wound healing, and successful infection treatment associated with Lutonix 014 DCB use vs. PTA, and whether these secondary endpoint results provide additional support for reasonable assurance of device effectiveness.

6. Additional Secondary Endpoint Evaluations

While the primary effectiveness endpoint of limb salvage and primary patency at 6 months showed a numerical benefit at 6 months, this benefit was not sustained at later timepoints. Some secondary endpoint analyses could be viewed as favorable to the Lutonix 014 DCB but have limitations. Please discuss the following:

a. The unplanned minor amputation rate favored the DCB arm at 36 months.

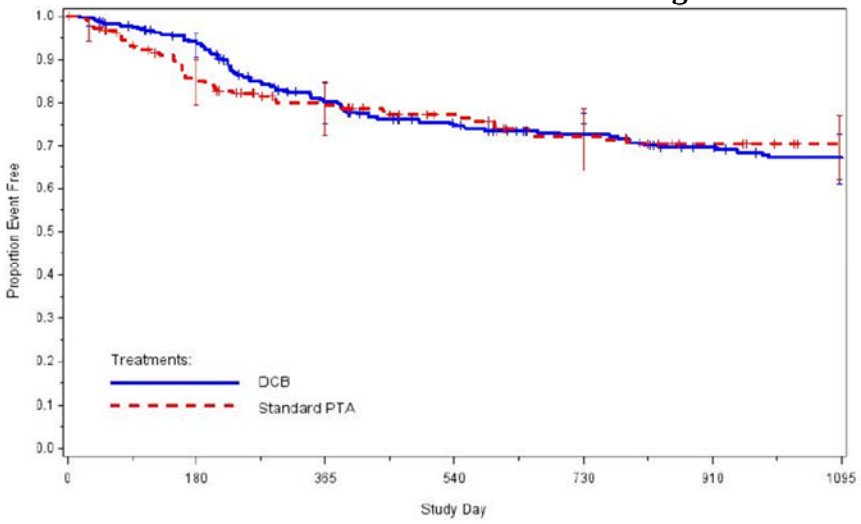
KM Estimates for Freedom from Unplanned Minor Amputation through 36 Months



At 6 months, there was a 0.9% lower rate, which improved to a difference of 3.7%, 5.8%, and 12% at 12, 24, and 36-months, respectively. However, there was overlap in the 95% CIs between treatment groups, and the KM curves only start to diverge after 730 days. Further, these data are limited by small sample sizes at the longer-term timepoints. Please discuss whether the unplanned minor amputation analysis provides important data supporting superior effectiveness of the Lutonix 014 DCB vs. PTA.

b. The freedom from CD-TLR rate at 6 months was numerically higher in the DCB arm (90.8%) vs. PTA (82.6%), although rates were similar thereafter through 36 months.

KM Estimates for Freedom from CD-TLR through 36 Months



Please discuss whether a lower TLR rate limited to 6 months provides additional support for reasonable assurance of device effectiveness.

7. Benefit/Risk

The Lutonix DCB failed to meet its primary endpoint at 6 months in the pivotal IDE trial, although a 10.5% improvement was noted compared to PTA. However, long term improvement was not observed, and actually favored the control arm through 36 months. It is unclear to FDA if the secondary endpoint analyses provide additional support for the effectiveness of the Lutonix 014 DCB. Although no safety concerns have been noted to date for this device, long-term data are limited, and the relevance of the late mortality signal detected for above-the-knee paclitaxel-coated devices to BTK paclitaxel-coated devices is uncertain. Various analyses of additional studies and data sources beyond the pivotal IDE were provided as additional support for the Lutonix DCB, although there were important limitations in these trials. Taken together, with the results of the pivotal IDE study and supplementary studies, please discuss whether the benefits of the Lutonix 014 DCB outweigh the risks to treat BTK vascular disease.

8. Post-Approval Study (PAS)

Note: This requested discussion item related to the proposed Post-Approval Study should not be interpreted to mean that FDA has made a decision or is making a recommendation on the approvability of this PMA. The presence of a post-approval study plan or commitment does not alter the requirements for premarket approval and a recommendation from the Panel on whether the benefits of the device outweigh the risks. The pre-market data must reach the threshold for providing a reasonable assurance of safety and effectiveness before the device can be found approvable and any post-approval study could be considered.

Post-approval studies are often required at the time of approval of a PMA to address remaining questions or provide information on the continued safety and effectiveness of the approved device. These studies are not intended to provide initial support for reasonable

assurance of safety and effectiveness, as that determination must be established prior to device approval. If a PAS is requested the sponsor has proposed a small, single arm, registry study to evaluate the TLR rate of the Lutonix 014 DCB at 12 months. Please discuss whether a new enrollment PAS would be appropriate to reduce further uncertainty associated with the effectiveness of the Lutonix 014 DCB. If so, please provide recommendations on the design of such a study and what types of questions could be answered.

VOTING

The Lutonix 014 DCB has a proposed indication for use (IFU) statement as follows:

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.

1. **VOTE: Based on data in the briefing materials and presentations at today's meeting, do you believe that there is reasonable assurance that the Lutonix 014 DCB is safe for the proposed Indications for Use? If not, please explain your concerns and provide suggestions as to the best way to obtain additional safety data.**

2. **VOTE: Based on data in the briefing materials and presentations at today's meeting, do you believe that there is reasonable assurance that the Lutonix 014 DCB is effective for the proposed Indications for Use? If not, please explain your concerns and provide suggestions as to the best way to obtain additional effectiveness data.**

3. **VOTE: Based on the data in the briefing material and presentations at today's meeting, do you believe that the benefits of the Lutonix 014 DCB outweigh the risks for the proposed Indications for Use? If not, please explain your concerns.**