Brief Summary
Circulatory System Devices Panel
of the
Medical Devices Advisory Committee
October 27, 2020

Neovasc Reducer System

Introduction:

The Circulatory System Devices Panel of the Medical Devices Advisory Committee to the Food and Drug Administration met on October 27, 2020, to discuss, make recommendations, and vote on information related to the Premarket Application (PMA) for the Neovasc Reducer System. The meeting was held virtually and was open to the public via webstream.

The sponsor has proposed the following Indications for Use:

The Reducer™ System is intended for patients suffering from refractory angina pectoris despite guideline directed medical therapy, who are unsuitable for revascularization by coronary artery bypass grafting (CABG) or by percutaneous coronary intervention (PCI).

Panel Deliberations/FDA Questions:

Question 1: Potential Patient Population

1. **When determining an acceptable indication for use statement, FDA must consider if the data provided supports a reasonable assurance of safety and effectiveness for a defined patient population. Please discuss whether the COSIRA trial identified and enrolled a defined patient population with refractory angina (despite optimal medical therapy).**

The panel discussed the limitations of the COSIRA study in defining a refractory angina patient population. Panelists acknowledged that it was difficult to optimize medical therapy, but the lack of information regarding the reasons some study subjects were on limited amounts of antianginal medications made it difficult to describe the population as "no option". The panelists concluded that the study identified participants with severe angina, but that there was not enough information to indicate the device for a specific population.

Question 2: Blinding, the Role of Placebo Effect, and Reducer Device Non-Responders

2a. Please discuss the robustness of the trial results given the lack of a blinding assessment throughout the course of the study and limited sample size.

2b. Given that some patients do not appear to receive any benefit from treatment (only 34.6% achieved primary endpoint success of a change in CCS of ≥ 2, and 28.8% demonstrated no change in CCS from baseline), we would like the Panel to discuss whether patients who are more likely to receive a significant clinical benefit can be identified prior to implantation of the Reducer device.

The panel credited the sponsor with conducting a sham-controlled interventional trial and acknowledged that they are logistically very difficult. Panelists were concerned that the sponsor could not explain the imbalance in missing information present in the control group versus the treatment group, or why there was significant missing information for secondary endpoints but none for the primary endpoint. Panelists suggested that the imbalance in missing information could indicate that control subjects aware of their treatment assignment were less inclined to participate in additional data collection. The panel concluded that blinding is critical when studying a placebo-responsive condition such as angina and that the lack of blinding assessment made the primary endpoint difficult to interpret. They noted that a more objective endpoint would have been helpful to mitigate these concerns.

Regarding patients who are likely to receive benefit, the panel concluded that due to the uncertainty regarding the device's mechanism of action and other study limitations, they could not determine which patients would be more likely to receive benefit from this device.

Question 3: Primary Effectiveness Endpoint

3a. Please discuss and comment on the subjective assessment of angina (change in Canadian Cardiovascular Society (CCS) grade) as a clinically meaningful correlate of ischemia to support a reasonable assurance of Reducer device effectiveness.

3b. Please discuss and comment on the overall primary effectiveness rate of 34.6%, given the permanent implant nature of this device and vulnerability of this no-option patient population.

The panel was concerned regarding the use of change in CCS grade as the sole primary endpoint for an ischemic refractory angina population. While the panelists discussed that angina symptoms, rather than ischemia, were the primary concern of many patients in this population, they concluded that because the device is intended to work by improving perfusion, evaluations such as exercise tolerance testing should be used to better evaluate ischemic change.

For the primary effectiveness rate, some panelists believed that the response rate was satisfactory, and others did not. Several panelists stated that the rate was good, but the small sample size was the larger problem, making it difficult to have confidence in the reproducibility of the COSIRA results. The panel concluded that the effectiveness rate needs to be balanced with safety and account for the placebo effect.

Question 4: Secondary Effectiveness Analysis

4a. Please discuss overall Reducer device effectiveness observed in the COSIRA trial, considering the small sample size (underpowered study for ischemia endpoints), high control group response rate, significant amounts of missing data for objective ischemia assessments, and lack of prespecified hypothesis tests for objective ischemia assessments.

4b. Please also discuss if additional premarket objective ischemia assessment data are needed to support Reducer effectiveness (e.g., primary endpoint of the COSIRA-II trial: Change in total exercise duration in modified Bruce treadmill exercise tolerance testing at 6 months).

The panel agreed with the concerns cited regarding the small sample size and unpowered secondary endpoints. The panel concluded that without randomization or blinding, the REDUCER I observational study data was of limited use in alleviating these concerns.

Regarding whether additional objective ischemia data was needed to support effectiveness, the panel requested to wait to discuss whether a new trial was needed until closer to voting.

Question 5: COSIRA Study Limitations

5a. Please discuss and make recommendations whether additional pre-market data from a randomized sham-controlled clinical study are needed to support the safety and effectiveness of the Neovasc Reducer System given the concerns and limitations with the currently available data.

5b. The demographics of the patients enrolled in the COSIRA trial had differences compared to the US refractory angina population (i.e., no Black or Hispanic patients enrolled and under-representation of females). Please discuss the applicability of the study results to the US refractory angina population and whether there is a need for additional clinical data on the safety and effectiveness of the Neovasc Reducer device in a more demographically representative population.

5c. Acknowledging that an understanding of the Reducer's mechanism of action is not a requirement for PMA approval, please discuss the principal data supporting the intended clinical benefit in your assessment of the strengths and limitations of the data supporting device effectiveness.

If you recommend additional premarket data to support a reasonable assurance of safety and effectiveness of the Reducer, please describe the types of studies (e.g., animal or human) that would be most useful. Please comment on and make recommendations regarding whether the recommended data could be obtained using a protocol similar to COSIRA-II.

Panelists discussed their concerns for this patient population that is difficult to treat and desperate for options, and how to weigh that against the lack of objective evidence of efficacy. Several panelists were concerned that approval would set a precedent and lead to the availability of multiple unproven therapies, ultimately making treatment decisions more difficult. There was consensus from the panel that additional premarket randomized clinical data was necessary.

Regarding whether the COSIRA data was applicable to a more diverse US patient population, the panelists agreed that the under-representation of women and minorities was not ideal. Some panelists believed the issue to be minor compared to the larger concerns with the trial, while others pointed out differences in angina symptoms between men and women and that it is inaccurate to state that no differences in response are likely across ethnic or racial groups since studies have not been done.

Regarding what types of studies would be most useful to support the safety and effectiveness of the Reducer device, the panel concluded a robust clinical study would be needed, and that animal studies could be useful to help identify patient subsets or further clarify the mechanism of action of the device.

Question 6: Benefit-Risk Relationship

6. Given the totality of the evidence regarding the effectiveness and safety profile of the device, please comment on the benefit-risk profile of this device.

The panel discussed the risks of the device. Several felt it was likely to be safe based on the evidence from COSIRA and REDUCER I. Others expressed concerns with the longer-term safety of the device, and with reports of device embolization in real world use. Panelists commented that the uncertainty of the benefit made it challenging to conclude a positive benefit-risk profile.

Question 7: Proposed Post-Approval Study

7. Please discuss and make recommendations regarding the Sponsor's proposal to perform a post-approval randomized sham-controlled trial. Please also discuss what alternative postmarket approval studies could provide the data need to support this device.

The Panel concluded that because they were in agreement that additional premarket clinical data were needed, a postmarket study would not be able to resolve their outstanding concerns.

Vote:

The Panel voted on the safety, effectiveness, and benefit-risk profile of the Neovasc Reducer™ System.

On Question 1, the Panel voted 14-4-0 (yes, no, abstain) regarding whether there is reasonable assurance that the Neovasc Reducer™ System is safe for use in patients who meet the criteria specified in the proposed indication.

On Question 2, the Panel voted 1-17-0 (yes, no, abstain) regarding whether there is reasonable assurance that the Neovasc Reducer™ System is effective for use in patients who meet the criteria specified in the proposed indication.

On Question 3, the Panel voted 3-13-2- (yes, no, abstain) regarding whether the benefits of the Neovasc Reducer™ System outweigh the risks for use in patients who meet the criteria specified in the proposed indication.

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