Questions for the Advisory Committee meeting for the Neovasc Reducer System for refractory angina patients

PANEL QUESTIONS/DISCUSSIONS

1. **Potential Patient Population**

Over 90% of COSIRA subjects were taking at least one antianginal medication (93.3%), and 36.5% were taking 3 or more at baseline. However, in a trial intended for a refractory angina population, ≥25% of subjects were only on 0 or 1 antianginal medications (Table 1).

Table 1. Antianginal Medications at Enrollment

Antianginal Medications – no.	Reducer N=52 (%)	Control N=52 (%)
0	4 (7.7)	3 (5.8)
1	10 (19.2)	10 (19.2)
2	18 (34.6)	23 (44.2)
3	18 (34.6)	12 (23.1)
>3	2 (3.8)	4 (7.7)

Table generated by FDA.

Additionally, at baseline, approximately 75% and 50% of subjects were taking ß-blockers or calcium channel blockers, respectively (Table 2). No justification was provided regarding the proportion of patients prescribed ß-blockers, nitrates, and Ca^{+} blockers in a refractory angina population. Also, no information was provided about medication compliance, or whether patients were on therapeutic or maximally tolerated doses.

Table 2. Cardiovascular Medications at Screening

Baseline Cardiovascular Medications	Reducer N=52 (%)	Control N=52 (%)
Subjects taking cardiac medication	52 (100.0)	52 (100.0)
ASA (Aspirin)	48 (92.3)	48 (92.3)
Statins	48 (92.3)	45 (86.5)
ß-blocker	40 (76.9)	40 (76.9)
Nitrates/NO donors	29 (55.8)	32 (61.5)
Clopidogrel	31 (59.6)	27 (51.9)
Calcium channel antagonist	29 (55.8)	26 (50)
ACE inhibitor	28 (53.8)	24 (46.2)
Diuretics	18 (34.6)	17 (32.7)
Angiotensin II antagonist	10 (19.2)	14 (26.9)
Molsidomine	9 (17.3)	9 (17.3)
Other lipid lowering drugs	7 (13.5)	10 (19.2)
Ivabradine (Procoralan)	4 (7.7)	5 (9.6)
Coumadin or other anti-vitamin K agent	2 (3.8)	3 (5.8)
Prasugrel	1 (1.9)	3 (5.8)

Baseline Cardiovascular Medications	Reducer N=52 (%)	Control N=52 (%)
Digitalis/digoxin	1 (1.9)	0 (0)

Question 1a: 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).

Regarding patient demographic and other baseline characteristics, the populations were similar between treatment groups (Table 3). The average age of the subjects was 67.8 years and ranged from 35 to 87 years. The majority of subjects (80.8%) were male and white (86.5%). The groups had comparable heart rates and blood pressure. However, the study included a limited number of female (19.2%) or minority (5.8%) patients.

Table 3. Baseline Demographic Data, Heart Rate and Blood Pressure

Baseline Characteristics	Reducer N=52	Control N=52
Mean Age, Range (years)	69.6 (51–87)	66.0 (35–84)
Gender		
Female – n (%)	8 (15.4)	12 (23.1)
Male – n (%)	44 (84.6)	40 (76.9)
Race		
Asian – n (%)	4 (7.7)	2 (3.8)
White – n (%)	44 (84.6)	46 (88.5)
Unknown – n (%)	4 (7.7)	4 (7.7)
Mean Weight (kg)	84.9	85.0
Mean Heart Rate (bpm)	64.9	65.4
Mean Systolic Blood Pressure (mmHg)	128.1	131.1
Mean Diastolic Blood Pressure (mmHg)	68.0	70.6

Question 1b: 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.

2. **Blinding, the Role of Placebo Effect, and Reducer Device Non-Responders**

Although subjects were blinded to their treatment group, there was no assessment of blinding success, such as a questionnaire asking subjects to identify the study arm to which they believed they were assigned. Additionally, the rate of missing data for Dobutamine stress echocardiography (DSE) at the 6-month follow up was notably higher in the control group,

which may indicate problems with the blinding. A notable placebo effect was also observed in the COSIRA control group, which presents challenges for interpreting the data given the limited sample size.

Question 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.

Question 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 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.

3. **Primary Effectiveness Endpoint**

A ≥2 CCS grade change at 6 months was the primary effectiveness endpoint of the COSIRA trial. Primary endpoint success was observed in 34.6% of subjects treated with the Reducer Group, while 15.4% of subjects achieved success in the Control group. In 28.8% of the Reducer Group and 57.7% of Control group, no change in CCS was observed. However, angina can be a placebo-responsive condition. Exercise tolerance tests (ETTs) provide an objective measure of functional capacity and myocardial ischemia. Other clinical trials evaluating anti-ischemic treatments have used ETT results as a primary effectiveness endpoint.

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

Question 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.

4. **Secondary Effectiveness Analysis**

In a secondary effectiveness analysis in COSIRA, ETTs (bicycle ergometry and dobutamine stress echocardiography) were used to objectively assess ischemia. Subjects in the Reducer group had numerically longer exercise durations (mean increase of 64.7 seconds vs. a mean increase of 4.3 seconds) and time to ST-segment depression vs. Control patients (76.3 seconds vs. 33.8s). However, the study was (1) underpowered to detect an improvement in functional ischemia between treatment groups, and (2) there was a substantial amount of missing information. For DSE data, missing data was noted in roughly 15% of the Reducer subjects, while about 30% was missing for the Control Subjects. Total exercise duration testing was missing in about 25% of all patients, and ST depression data was missing from 70-88% of patients. These two factors impact the conclusions that may be drawn from these ischemia data.

Question 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.

Question 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).

5. COSIRA Study Limitations

As discussed in FDA's executive summary, there are limitations to the currently provided data set. These limitations include, but are not limited to:

- Lack of a non-exercise primary effectiveness endpoint and no pre-specified hypothesis tests for objective secondary endpoints;
- Small sample size;
- Significant missing secondary endpoint information;
- Lack of a formal assessment for coronary sinus (CS) stenosis or severity;
- Lack of evidence of a CS pressure gradient across the device;
- High placebo response rate.

In addition, the Reducer device is intended to create a CS stenosis resulting in a functionally significant increase in CS pressure gradient that may reduce myocardial ischemia by redistributing subepicardial blood flow to the subendocardium. However, in vivo animal studies were not sufficient to confirm tissue coverage to restrict CS blood flow to the Reducer's central orifice. Further, neither in vivo animal nor clinical data were provided to show that the Reducer device performed as intended, because there were no adequate studies that assessed:

- The presence or severity of a CS stenosis;
- A CS pressure gradient across the device; or
- The association of a CS stenosis or a CS pressure gradient with reduced angina or ischemia.

Question 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.

Question 5b: 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 from using a protocol similar to COSIRA-II.

6. **Benefit/Risk**

Question 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.

7. **Proposed 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.

In response to the concerns identified by FDA during the initial round of review, the sponsor has proposed the following for a potential PAS:

> *Neovasc has committed to do a post-approval randomized, double-blind, sham-controlled study in a country where Reducer is not approved to allow the collection of data to reduce the amount of remaining uncertainty FDA may have.*

The FDA may require a post-approval study (or studies) at the time of approval of a PMA to provide information on the continued safety and effectiveness of the approved device. These studies are not intended to provide a reasonable assurance of safety and effectiveness, as that determination must be established prior to device approval, and are typically not randomized. As the sponsor has identified a "no-option" patient population, FDA is concerned that after making a determination that there is a reasonable assurance that the device is safe and effective, it may not be appropriate to mandate a new trial as a condition of device approval in which patients who lack alternative treatments would be randomized to a sham control.

Question 7a: 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.

VOTING (not included in the Panel Pack Set of Questions)

<u>Proposed Indications for Use Statement</u>:

The Neovasc Reducer System has a proposed indication for use (IFU) statement as follows:

> *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).*

8. **VOTE: Based on data in the briefing materials and presentations at today's meeting, do you believe that there is reasonable assurance that the Neovasc Reducer System is safe for use in patients determined to have refractory angina and who are unsuitable for revascularization by CABG or PCI as specified in the proposed indication? If not, please explain your concerns and provide suggestions as to the best way to obtain additional safety data**.

9. **VOTE: Based on data in the briefing materials and presentations at today's meeting, do you believe that there is reasonable assurance that the Neovasc Reducer System is effective for use in patients determined to have refractory angina and who are unsuitable for revascularization by CABG or PCI as specified in the proposed indication? If not, please explain your concerns and provide a brief discussion as to the best way to obtain additional effectiveness data**.

10. **VOTE: Based on the data in the briefing material and presentations at today's meeting, do you believe that the benefits of the Neovasc Reducer System outweigh the risks for use in patients determined to have refractory angina and who are unsuitable for revascularization by CABG or PCI as specified in the proposed indication? If not, please explain your concerns.**