FDA Executive Summary

Prepared for the October 27, 2020 Meeting of the
Cardiovascular Devices Panel
Meeting to be held Virtually

Premarket Approval (PMA) P190035
Neovasc Medical, Inc.
Neovasc Reducer™ System

Office of Cardiovascular Device
Office of Product Evaluation and Quality
Center for Devices and Radiological Health
Food and Drug Administration

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1 Introduction

This is FDA's Executive Summary of the premarket approval (PMA) P190035 application from Neovasc Medical for the Neovasc Reducer™ System (Reducer) for the treatment of patients with 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). This Advisory Committee meeting is being held for the Panel to discuss and make recommendations regarding the safety and effectiveness of this device based on the available data. This document includes a brief review of the treatment of refractory angina, a description of the device, a review of non-clinical studies, and the presentation of clinical data provided as part of the PMA application.

1.1 Clinical Background

The European Society of Cardiology Joint Study group on the Treatment of Refractory Angina defined refractory angina as follows:

> "*Refractory angina pectoris is a chronic condition characterized by the presence of angina caused by coronary insufficiency in the presence of coronary artery disease which cannot be controlled by a combination of medical therapy, angioplasty and coronary bypass surgery. The presence of reversible myocardial ischaemia should be clinically established to be the cause of the symptoms. Chronic is defined as a duration of more than 3 months*". (Mannheimer et al. 2002).

In 2009, the Canadian Cardiovascular Society issued the following definition of refractory angina:

> "*Refractory angina is a persistent, painful condition characterized by the presence of angina caused by coronary insufficiency in the presence of coronary artery disease which cannot be controlled by a combination of medical therapy, angioplasty/percutaneous interventions, and coronary bypass surgery. While the presence of reversible myocardial ischemia must be clinically established to be the root cause, the pain experienced may arise or persist with or without this ischemia. Chronic is defined as persisting for more than 3 months.*"

Class III or IV refractory angina patients have severe impairment in their quality of life, psychological distress, and significant activity restrictions (Gallo et al. 2009).

The true prevalence of refractory angina is difficult to determine as the condition has not been well studied. One estimate is that as many as 1 million people in the United States (US) are affected (Grise and Verma 2009). Within the refractory angina patient population, there is a smaller sub-population of "no-option" Canadian Cardiovascular Society (CCS) functional Class III or IV refractory angina patients who are severely limited in their ability to perform activities of daily living. The size of this subpopulation has been the subject of different estimates. Williams et al. (2010) assessed 493 consecutive angina patients, of whom 6.7% were characterized as "no-option" (symptoms despite optimal medical therapy and not candidates for revascularization). In the US, the number of no-option refractory angina patients has been estimated to be between 26,000 and 52,000 (Velagapudi et al. 2019). A wide range of 1-year mortality rates have been reported. Data from a refractory angina clinic at the Minneapolis Heart

Institute reported a mortality rate of 3.9% at 1 year and 28.4% at 9 years. With respect to therapeutic options for patients with refractory angina, other FDA-approved options include enhanced external counter pulsation (EECP) and myocardial laser revascularization by surgical (TMR) or percutaneous (PMR) techniques. Neither of these approaches are widely used.

The decision to classify an angina patient as refractory and not to pursue revascularization is difficult and varies depending on patient-specific characteristics and available medical expertise (Kiernan et al. 2009; Jolicoeur et al. 2012). This variability makes it challenging to reach consensus on why or when a patient is unsuitable for revascularization (Kornowski 2010; Jolicoeur et al. 2012).

The Neovasc Reducer System, which is the subject of this meeting, is designed to be implanted into the coronary sinus. It is hypothesized to narrow the coronary sinus, increasing backpressure and aiding in redistributing collateral blood flow into ischemic myocardial territories (see Section 4 for a discussion of the device's hypothesized mechanism of action). If approved, the Neovasc Reducer System will be the first coronary sinus narrowing device in the US. The Panel will be asked to help determine if sufficient clinical evidence has been provided for the Neovasc Reducer System to support a determination of reasonable assurance of safety and effectiveness for the proposed indications for use based primarily on the prospectively collected data obtained from the COSIRA trial, which was conducted outside the US (OUS).

2 Proposed Indications for Use

Neovasc proposes the following indications for use (IFU) statement for the Reducer™ System:

> *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 Question: The Panel will be asked to comment on whether a reasonable assurance of safety and effectiveness has been established for the proposed IFU based on totality the of the evidence presented herein. Additionally, the Panel will be asked to comment and make recommendations on whether the evidence provided adequately defines the patient population to support the proposed IFU.

3 Device Description

The Neovasc Reducer System consists of an implantable Reducer device pre-mounted on a balloon catheter delivery system. The Reducer System is available in one model size and is a sterile and single-use device. The device is designed to establish a narrowing in the CS, which is intended to improve perfusion to ischemic myocardium in the presence of reversible ischemic heart disease to alleviate the symptoms of refractory angina. Device implantation is performed through percutaneous access through the right internal jugular vein into the CS. The pre-mounted balloon catheter is inflated to help form the device's intended shape and apposition with the CS

wall. The balloon catheter is then deflated and removed from the CS, leaving the device permanently implanted. See Figure 1A and Figure 1B.

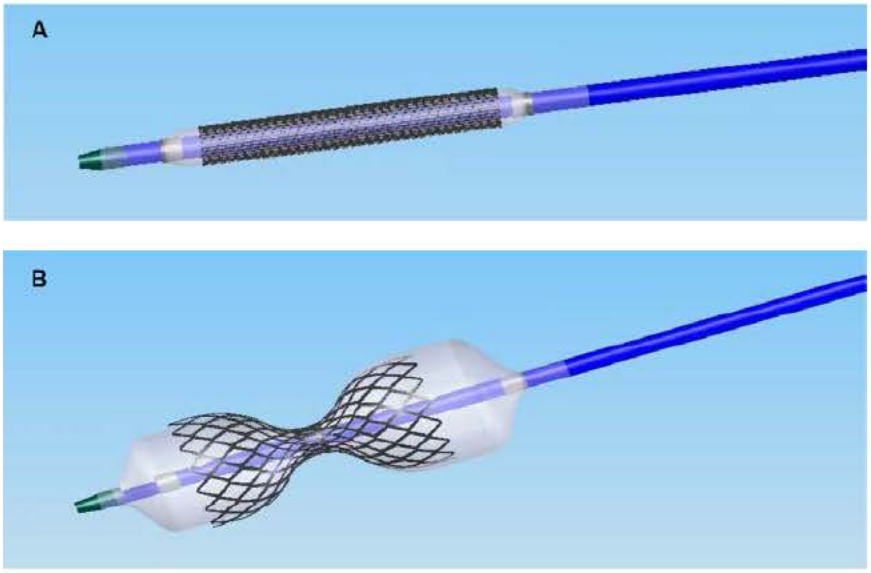
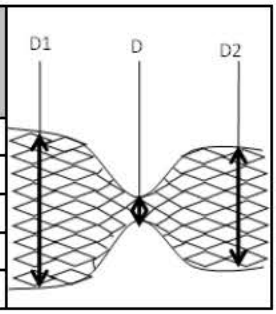


Figure 1. The Neovasc Reducer: (A) Crimped and (B) Expanded

3.1 Reducer

The Reducer (stent) is a balloon expandable vascular/coronary device manufactured from surgical grade 316L stainless steel seamless tubular mesh, laser cut into a pre-specified geometric pattern with no welding points and flexible longitudinal struts, with smooth internal and external surfaces and rounded edges intended to prevent damage to the vessel wall. The Reducer is available in a single model designed to fit a range of anatomies. The Reducer is intended for CS dimensions from 9.5 mm to 13 mm in diameter at the proximal implant site. The device has an overall length of 25.4 mm. Its final profile is determined by the inflation pressure of the semi-compliant deployment balloon. Table 1 lists the typical outer diameter (OD) of the Reducer at the defined locations when inflated to the indicated pressures (atm).

Table 1. Reducer Compliance Chart

Pressure [atm]	D1 – Proximal Outer Diameter [mm]	D – Neck Outer Diameter [mm]	D2 – Distal Outer Diameter [mm]	
2	12.0	3.0	9.6	
3	12.7	3.0	10.2	
4 – Nominal	13.3	3.0	10.7	
5	13.6	3.0	11.1	
6 – Rated Burst	13.9	3.1	11.5	

3.1.1 Previous Device Iterations

While the sponsor is requesting PMA approval for the device described above, the Reducer device used in the First-in-Human (FIH) clinical study was different than the current generation device. The Neovasc Reducer System underwent a design revision prior to being finalized in its current state in 2009. The Coronary Sinus Reducer for Treatment of Refractory Angina (COSIRA) trial was initiated in 2010 in Europe and Canada using the current version. The largest difference between the initial FIH design and the current design used in COSIRA was a change to the catheter delivery system, but modifications were also made to the implant portion of the device. The Reducer used in the FIH study was hand-crimped by the physician onto a commercially available 11 Fr cylindrical shaped balloon catheter. For the model studied in COSIRA and proposed under the PMA, the Reducer was pre-mounted to a dedicated 9 Fr hourglass-shaped balloon delivery catheter, allowing the neck stiffness of the Reducer to be reduced.

During deployment, the proximal and distal ends of both Reducer models are apposed to the CS wall, with differences in the narrowed-neck region only. The neck stiffness was reduced by increasing the length of the axial cuts in the neck area of the device. To maintain the substantially same strut density and wall contact in this region, two crowns were added within the neck of the device, while still maintaining 39% of the overall neck region strut density (by surface area). To avoid overlapping of the edges when crimped due to the larger number of crowns, the radius of the edge connection between the struts was also reduced slightly in the COSIRA model, as shown in Figure 2.

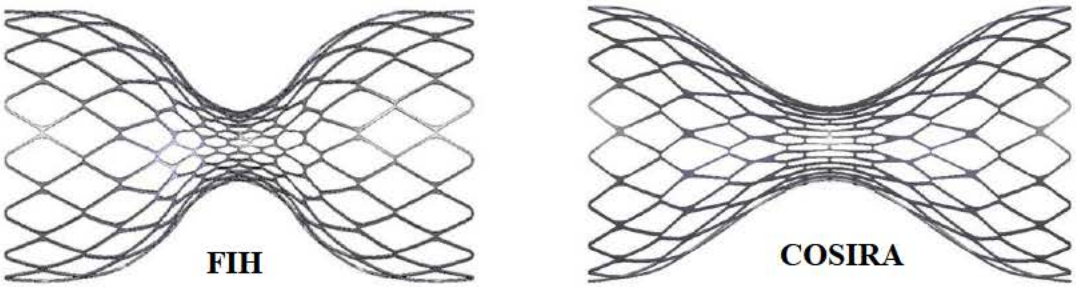


Figure 2. Comparison of Reducer Models

3.2 Delivery System

The Reducer delivery catheter is an over-the-wire catheter with a semi-compliant deployment balloon. The balloon is constructed of polyether block amide and is shaped like an hourglass when expanded (Figure 3). The proximal and distal portions of the balloon have diameters that are different with respect to each other, to conform to the taper of the CS vessel wall. The balloon catheter is also constructed of the same polyether block amide materials and contains two separate lumens: one for a 0.035"guidewire to advance and withdraw the Reducer and delivery catheter, and the second for balloon inflation and deflation.

Figure 3. Reducer Balloon Catheter (expanded)

4 Reducer CS Implantation and Principle of Operation

The Reducer is introduced into the CS via right heart catheterization through the internal jugular vein. The intended location for Reducer implantation is proximal to the upward curve of the CS, 2-4 cm distal to the right atrial ostium, as shown in Figure 4. After the Reducer is implanted in the CS, the sponsor proposes that local flow disruption and vascular reaction will induce a neointimal proliferative response that will occlude the fenestrations in the metal mesh. The central orifice of the device is intended to remain patent and becomes the sole path for blood flow through the CS, leading to the development of an upstream pressure gradient resulting in the redistribution of blood from the less ischemic epicardium to the ischemic endocardium.

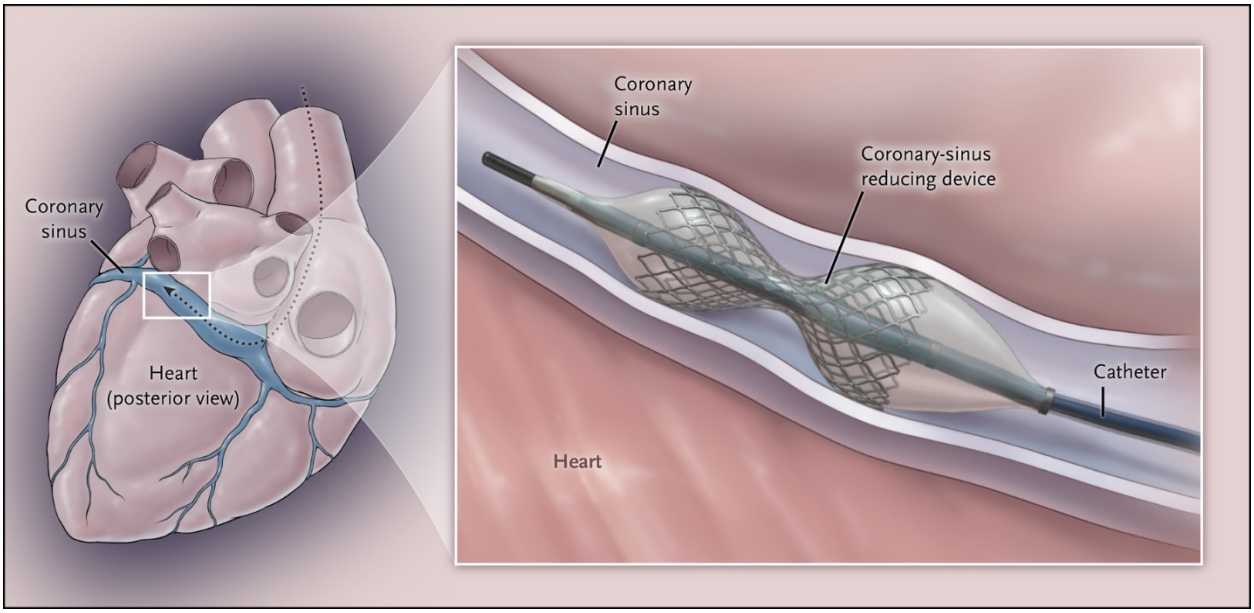


Figure 4. Location for Reducer Implantation in CS. (Verheye et al. 2015)

When coronary arteries are severely stenosed or occluded, blood flow decreases, and pain is caused by myocardial ischemia. The mechanism by which the Reducer might reduce myocardial

ischemia and reduce the frequency of anginal episodes is unknown. During myocardial ischemia, there is some evidence that myocardial blood flow is preferentially directed to the subepicardial regions and reduced in the subendocardium. It has been postulated that a pressure gradient created in the coronary sinus may reverse this mal-distribution via dilatation of the subendocardial microvasculature, which increases subendocardial perfusion. However, there is only limited evidence supporting this pathophysiological mechanism.

A legacy operation of the 1950s, the Beck procedure has been cited as the basis for the development of the Reducer device. Prior to the development of coronary bypass graft surgery, the Beck procedure was used to treat angina. The operation consists of partial occlusion of the coronary sinus (to 3 mm in diameter) *plus* the production of a chemically-induced pericarditis. Uncontrolled studies of the Beck procedure showed a reduction in angina frequency (Beck and Leighninger 1955), but studies using exercise tolerance tests showed that the operation resulted in no evidence of an improvement in either the amount of exercise possible before angina develops or in the electrocardiographic changes of myocardial ischemia, raising the possibility of a placebo effect (Sandler, Slesser, and Lawson 1967).

In addition to an absence of convincing evidence that CS narrowing was effective in increasing subendocardial perfusion and reducing ischemia and angina, there are several outstanding questions regarding the CS anatomic and physiologic changes needed to provide patient benefit, and whether the Reducer reproducibly creates these CS modifications. The Reducer is designed to produce a focal luminal narrowing resulting in a pressure increase within the CS. However, for CS interventions of this type, neither the (1) degree of CS stenosis nor the (2) required pressure gradient within the CS needed to potentially increase subendocardial perfusion has been established. In FDA's opinion, and as discussed in this Summary, the Reducer in-vivo animal studies and clinical studies do not provide additional insights to address the degree of CS stenosis or the CS pressure gradient associated with clinical benefits. Specifically, the in-vivo animal studies and the clinical studies have important limitations that raise questions whether the Reducer performs as intended to produce (1) a clinically meaningful functional CS stenosis and pressure gradient, (2) increased myocardial blood, and (3) reduced myocardial ischemia.

Importantly, as Konigstein et al. (2018) notes, patients in whom angina is only due to ischemia arising from the right coronary artery (RCA) are less likely to improve following Reducer implantation, as the insertion of the vein draining the RCA territory (middle cardiac vein) in the CS is next to the ostium of the CS. The preferred Reducer implantation target site is more distal into the CS, about 2 cm away from the ostium; therefore, any pressure gradient created by the narrowing would likely not affect the middle cardiac vein (Konigstein, Giannini, and Banai 2018).

<u>FDA Comment</u>: While the sponsor has proposed a principle of operation for the Reducer via a neointimal proliferative response within the CS that occludes the fenestrations in the metal mesh, there is limited pre-clinical or clinical evidence to support this mechanism of action. Additionally, as noted in the New England Journal of Medicine publication of the COSIRA trial, the physiological rationale for a beneficial effect of increased coronary sinus pressure remains unclear (Verheye et al. 2015). The COSIRA study authors indicated that additional work is needed to properly understand the complete principle of operation to better identify potential responders and non-

responders. Since the publication of the COSIRA study, important questions regarding the proposed mechanism of action for this device remain. Keeping in mind that an understanding of the Reducer's mechanism of action is not a requirement for PMA approval, the Panel may wish to consider the uncertainties regarding the device's mechanism of action and the scientific plausibility of clinical benefit when assessing the totality of the clinical data.

5 Regulatory History

An Investigational Device Exemption (IDE) application for the Reducer System was initially submitted to FDA in 2010 ([(b) (4)]) for the COSIRA trial. Neovasc and FDA did not agree on certain aspects of the study design, and Neovasc conducted the COSIRA trial OUS.

Neovasc submitted a second original IDE [(b) (4)] application on September 14, 2016, this time for the proposed COSIRA-II study. As indicated by the sponsor, the COSIRA-II trial was to build on the information obtained during the OUS COSIRA study and was intended to provide pivotal US market entry data for the Reducer System. COSIRA-II was designed to be a 380 subject, multicenter, randomized (1:1 randomization ratio), double blind, sham-controlled clinical trial with up to 35 investigational centers across North America.

The COSIRA-II primary effectiveness endpoint was the change from baseline in total exercise duration in a modified Bruce treadmill exercise tolerance test at 6 months post-procedure. The safety endpoint was the rate of occurrence of a composite of death, myocardial infarction (MI), pericardial effusion requiring surgical or percutaneous intervention, device embolization, or BARC 3 or 5 bleeding within 12 months post-procedure.

After several rounds of review, FDA determined that there were no safety concerns precluding COSIRA-II initiation, and the IDE was approved on November 3, 2017. FDA provided a "Study Design Consideration"[1] indicating that the sponsor should consider including an adjunctive imaging sub-study. An imaging study was requested because FDA had determined that outstanding questions remained regarding the Reducer's ability to provide sustained benefit. FDA additionally believed that due to the novelty of this device and because of the limitations identified in the animal study data (see Section 6.4), a more direct observation of the device's performance in the vasculature could help to leverage information collected on prior device iterations and help to address any potential limitations or uncertainties observed during the

[1] As of July 9, 2012, the FDA Safety and Innovation Act (FDASIA) specified that IDE clinical studies cannot be disapproved because the investigation may not support a marketing application or because another investigation may be needed. Since FDASIA was enacted, FDA has been conveying concerns related to the trial design as "Study Design Considerations" as an attachment to IDE decision letters, which are not required for the sponsor of the study to address to meet the IDE requirements, even if FDA does not believe the study designs is adequate to support a future marketing application. If the sponsor completes their proposed study even though there were outstanding FDA concerns regarding the study design, the FDA will still review the data generated from the clinical study, considering the previously conveyed study design considerations, and decide as to whether the data supports a reasonable assurance of safety and effectiveness for the medical device and whether the PMA marketing application can be approved for the proposed indications for use.

conduct of the COSIRA-II study. However, the sponsor opted not to initiate the COSIRA-II study. The protocol synopsis for this trial is provided in Appendix D.

The primary clinical data submitted in support of the current PMA (P190035) is from the original COSIRA trial that was conducted OUS and was designed without FDA input or agreement that the results for this trial could potentially support a future PMA submission.

The Reducer System received CE Mark in November 2011, and as of August 12, 2019, 2044 units have been distributed outside the US. The Reducer System is marketed in 17 countries including Austria, Belgium, Denmark, Finland, Germany, Israel, Italy, Norway, Poland, Portugal, Saudi Arabia, Slovenia, Spain, Sweden, Switzerland, the Netherlands, and the United Kingdom. The device has not been withdrawn from the market in any country for any reason related to the safety or effectiveness of the device.

5.1 Breakthrough Device Designation

The Breakthrough Devices Program[2] is a voluntary program for certain medical devices that provide for more effective treatment or diagnosis of life-threatening or irreversibly debilitating diseases or conditions. This program is intended to provide patients and health care providers with timely access to these medical devices by speeding up their development, assessment, and review, while preserving the statutory standards for premarket approval, 510(k) clearance, and De Novo marketing authorization, consistent with the Agency's mission to protect and promote public health. The program offers manufacturers an opportunity to interact with the FDA's experts through several different program options to efficiently address topics as they arise during the premarket review phase.

On August 20, 2018, the sponsor requested that the Reducer System be granted a Breakthrough Device designation for "no-option" refractory angina patients. FDA determined that the Reducer System met the criteria for inclusion in the program because it presented a novel technology with *the potential* to provide clinical benefit and symptomatic relief to "no-option" patients suffering from chronic refractory angina.

FDA granted the Reducer Breakthrough Device designation on October 9, 2018. Upon receipt of the designation, the sponsor asked for feedback about whether the trial data obtained from COSIRA could support the approval of a PMA. In written feedback provided on February 14, 2019, FDA indicated that based on the previously collected data from the FIH, COSIRA, and REDUCER-I trials provided as part of the sponsors IDE application (b) (4), additional premarket randomized clinical data would be necessary to provide a reasonable assurance of safety and effectiveness.

FDA Comment: It is important that the Panel be aware that while the Breakthrough Device Program offers increased communication and collaboration with FDA, it does not

[2] Guidance on the Breakthrough Device Program can be found on the FDA website at: https://www fda.gov/media/108135/download

modify or reduce the statutory requirement for device approval. The currently available Reducer system data are still required to demonstrate a reasonable assurance of safety and effectiveness for its intended population[3].

5.2 Uncertainty Considerations and Least Burdensome Approach

In August of 2019, FDA issued the guidance document "Consideration of Uncertainty in Making Benefit-Risk Determinations in Medical Device Premarket Approvals, De Novo Classifications, and Humanitarian Device Exemptions."[4] This document outlines the agency's current approach to considering uncertainty in making benefit-risk determinations to support FDA premarket decisions for PMAs with specific considerations for Breakthrough Device designations. As with all devices subject to a PMA, Breakthrough Devices must still meet the statutory requirement of reasonable assurance of safety and effectiveness at the time of approval.

In all premarket approval decisions, there is some degree of uncertainty about the benefits and risks of a device. For Breakthrough Devices, FDA may accept more uncertainty of the benefit-risk profile if the uncertainty is sufficiently balanced by other factors, including the probable benefits for patients to have earlier access to the device. This greater uncertainty may be addressed through multiple mechanisms such as timely postmarket data collection, transparency, and accountability. However, approaches to address increased uncertainty may only be accomplished if the statutory standards for premarket approval (i.e., a reasonable assurance of safety and effectiveness based on the available data) have been met.

In addition to considering increased uncertainty for Breakthrough Devices, FDA also applies a least burdensome approach to its review process. The least burdensome regulations, in accordance with the 21st Century Cures Act (Cures Act), require FDA to "consider the role of postmarket information in determining the least burdensome means of demonstrating a reasonable assurance of device safety and effectiveness" for PMAs. Least burdensome provisions do not, however, alter the applicable regulatory standards for marketing authorizations.

FDA Comment: In considering a Breakthrough Device designation, FDA determined that the Reducer is intended to treat patients with an irreversibly debilitating condition

[3] 21 CFR 814.20(b)(3)(vi) states that as part of a PMA application, the sponsor shall include: "Conclusions drawn from the studies. A discussion demonstrating that the data and information in the application constitute valid scientific evidence within the meaning of 860.7 and provide reasonable assurance that the device is safe and effective for its intended use. A concluding discussion shall present benefit and risk considerations related to the device including a discussion of any adverse effects of the device on health and any proposed additional studies or surveillance the applicant intends to conduct following approval of the PMA."

[4] Additional information on FDA's guidance document regarding considerations of uncertainty can be found at: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/consideration-uncertainty-making-benefit-risk-determinations-medical-device-premarket-approvals-de

where there are no approved or cleared alternatives (i.e., for "no option" refractory angina patients). However, a breakthrough device designation does not alter the statutory PMA requirement that the device must demonstrate a reasonable assurance of safety and effectiveness. Rather, the designation highlights that the potential benefits of earlier access to the device should be weighed against the potential risks associated with greater uncertainty in the data to support the submission, along with the potential to reduce uncertainty with postmarket data collection[5].

5.3 Determination for an Advisory Committee Request

While FDA reserves the right to refer a PMA application to an advisory panel on its own initiative, the regulations[6] also afford the applicant the right to request a panel meeting to review and help make recommendations regarding PMA applications. In this case, the sponsor has requested that: "*if FDA, after reviewing the evidence provided in this submission, has remaining uncertainty that the sponsor has met the statutory requirement for reasonable assurance of safety and effectiveness, Neovasc requests review at an advisory panel meeting.*" Therefore, FDA has requested guidance from the Panel regarding the totality of the data provided in determining whether there is a reasonable assurance of safety and effectiveness.

6 Pre-clinical Studies

6.1 Design Verification and Validation

The Reducer implant and delivery system underwent appropriate testing for design verification and validation, including long term durability and corrosion testing. Testing included material characterization along with implant and delivery system dimensional and functional attributes. The device passed all established acceptance criteria, with additional information regarding this testing provided in Appendix C.

6.2 Biocompatibility

Biocompatibility testing of the sterile finished Reducer System was performed in accordance with BS EN ISO 10993-1, Biological Evaluation of Medical Devices – Part 1: Evaluation and Testing. The device passed all established acceptance criteria, with additional information regarding this testing provided in Appendix C.

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[5] Additional information on FDA's guidance document regarding balancing premarket and postmarket data collection for PMA devices can be found at: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/balancing-premarket-and-postmarket-data-collection-devices-subject-premarket-approval

[6] 21 CFR 814.44(a) states that FDA may refer the PMA to a panel on its own initiative, and will do so upon request of an applicant, unless FDA determines that the application substantially duplicates information previously reviewed by a panel. If FDA refers an application to a panel, FDA will forward the PMA, or relevant portions thereof, to each member of the appropriate FDA panel for review.

6.3 Sterilization Packaging, and Shelf-Life

The Reducer System is sterilized using Ethylene Oxide (EO) with a sterility assurance level (SAL) of 10^{-6} validated per BS EN ISO 11135. Ethylene oxide residuals meet limits in accordance with ISO 10993-7:2008.

Package integrity has been demonstrated for the Reducer System after sterilization and in accordance with ISO 11607-1:2009/A1:2014. Samples of the Reducer System were subjected to accelerated aging and evaluated through functional testing to ensure the product continues to meet specifications. Real-time shelf-life testing was conducted on the Reducer System and packaging to support a labeled shelf life of 24 months.

6.4 Animal Studies

The sponsor provided limited data from three non-Good Laboratory Practice (non-GLP) animal studies of the Neovasc Reducer System in both ischemic and non-ischemic models. The first two studies used the earlier version of the device, while the third study used the current version. The differences between the two device versions are described in Section 3.1. The animal investigations are summarized below according to the information submitted for FDA review. As part of the PMA major deficiency letter provided to the sponsor on March 30, 2020, FDA communicated that a new GLP animal study may be needed because there were many outstanding concerns with the non-GLP studies that the existing clinical data do not adequately address. These concerns include problems with the quality and consistency of the data, inadequate documentation, unclear timelines, and concerns regarding incomplete tissue coverage and endothelialization of the Reducer device.

6.4.1 Preliminary Porcine Animal Study

The preliminary animal study, initiated December 1, 2002, was a double-arm study in 34 mini-swine with the objective of evaluating the safety, efficacy, and applicability of coronary sinus narrowing with the earlier version of the Reducer System in a simulated clinical use environment. Prior to implantation of the Reducer, 22 of the 34 animals were implanted with an ameroid constrictor device to achieve gradual occlusion of the left circumflex coronary artery (LCX). No ameroid constrictor was implanted in the remaining 12 non-ischemic pigs. After 6 weeks, coronary angiography was performed to evaluate occlusion of the LCX. At 6- to 9-weeks post implantation of the constrictor, myocardial function and the presence of reversible myocardial ischemia were evaluated via transthoracic echocardiography (TTE), dobutamine stress echocardiography (DSE), and myocardial contrast echocardiography (MCE). Implantation of the Reducer was performed in 4 of 8 pigs in which ischemia was induced, and the remaining 4 did not receive the device. In non-ischemic animals, the Reducer was implanted in 14 pigs implanted with an ameroid constrictor and 12 pigs that did not receive a constrictor. Figure 5 shows the animal group assignments.

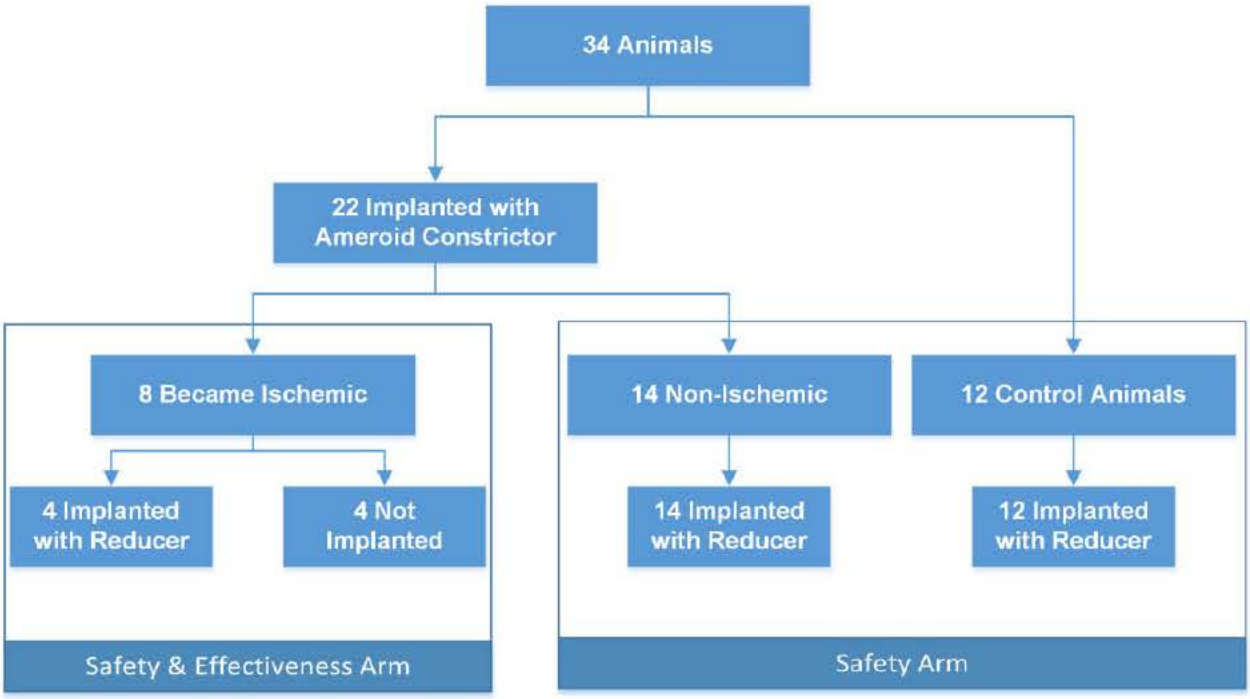


Figure 5. Preliminary Animal Study Group Assignments

May 13, 2009 final report: 30 Reducers were implanted in the coronary sinuses of 30 animals. The sponsor reported that patency and adequate drainage of the CS through the 3 mm diameter neck of the Reducer were observed. However, these findings were not able to be confirmed by FDA due to the lack of individual animal records that documented the delivery and implantation of the device by the appropriate personnel, angiograms at different time points, and the procedural evaluation details. It was also reported that in the ischemic Reducer group, improvement in both left ventricular contractility and myocardial perfusion were observed at 6 weeks in 4 out of 4 animals, but these findings were also not confirmed by FDA in our review of the study report data.

In the ischemic no-Reducer group (n=4), two animals were reported to be available for follow-up and underwent 6-week evaluations that did not show improvement in left ventricular contractility or myocardial perfusion (Table 2). One of the 2 animals evaluated died immediately after the 6-week evaluation. The remaining 2 animals in the ischemic no-Reducer group died prematurely prior to the 6-week evaluation. There was no adequate evaluation and post-mortem data available for all the animals in the ischemic no-Reducer group.

Table 2. Evaluation of the Reducer in Animals with Ameroid-Induced Myocardial Ischemia

Group Type	6-Week Follow-Up		6-Month Follow-Up	
	DSE	Complications	DSE	Complications
Reducer Group (n=4)	Improved	No	Stable improvement	No

Group Type	6-Week Follow-Up		6-Month Follow-Up	
	DSE	Complications	DSE	Complications
No-Reducer Group (n=4)	Not performed (2) Ischemic (2)	Died (3)* No (1)	Ischemic	Ischemic

* Deaths were due to pulmonary edema (2) and ventricular fibrillation (1).

In the non-ischemic pigs, all 26 animals with Reducer implants survived to term with no complications and complete CS patency at sacrifice as measured by coronary angiography. The mean trans-Reducer pressure gradient measured 15 minutes post implantation was 3.71±1.75 mm Hg, and the mean trans-Reducer pressure gradient measured 2 to 6 months following implantation was 2.83±1.47 mm Hg. The pressure gradient results show a low trans-Reducer pressure gradient at 2 to 6 months, which was also paradoxically lower than the gradient at the time of device implant. The finding is opposite of the intended effect of the device. When this concern was presented to the sponsor, they stated that a pressure gradient across the Reducer is needed for the device to be effective.

In the histological evaluation of the treated coronary sinus, the sponsor reported that there was a low incidence of mural disruption, inflammation, granulomatous reaction, and incomplete endothelialization. The transverse proximal, middle, and distal sections of the treated coronary sinus showed luminal narrowing, and some sections showed focal organizing thrombus on the stent surface.

6.4.2 Pivotal Porcine Animal Study

The pivotal animal study was a single-arm study initiated on January 26, 2009 that used the current version of the Reducer. The objective of the study was to "evaluate and confirm the performance of the procedure used for the deployment and safety of implanting the Reducer in the coronary sinus (CS) of pigs." This study included the use of two farm pigs and 11 mini-pigs (40 kg) (n=13 total animals) and 16 Reducer implantations in the CS.

Two study sites were used: Technion University, Haifa, Israel and CBSET, Lexington, MA. Multiple Reducers were intentionally implanted in three animals to evaluate for device performance and handling. Tissue harvest time points are shown in Table 3.

Table 3. Animals Sacrificed at Each Time Point

	Acute	24 Hours	57 Days	104 Days	140 Days
Number of animals	4	2*	2	3	2

* The two animals sacrificed at 24 hours were farm pigs; all others were mini-pigs.

The sponsor reported that the device remained securely crimped on the delivery system after extensive manipulations. There were no premature detachments of the Reducer from the delivery system. CS patency was present in all CS at the time of animal sacrifice. There was no Reducer migration in animals where only one device was implanted and when the device was placed at the appropriate location.

6.4.2.1 Histopathology

A device endothelization assessment was limited to three sections of each device (proximal, mid, and distal). The endothelialization score was based on the extent of the circumference of the lumen showing coverage with endothelial cells: 0 = absent; 1 = < 25% of circumference covered; 2 = 25% to 75%; 3 = >75% to <100%; and 4= 100%, confluent. Histopathological assessment was performed on minipigs from the 57-day (2 months, n=2), 104-day (3 months, n=3), and 140-day (5 months, n=2) groups (Figure 6).

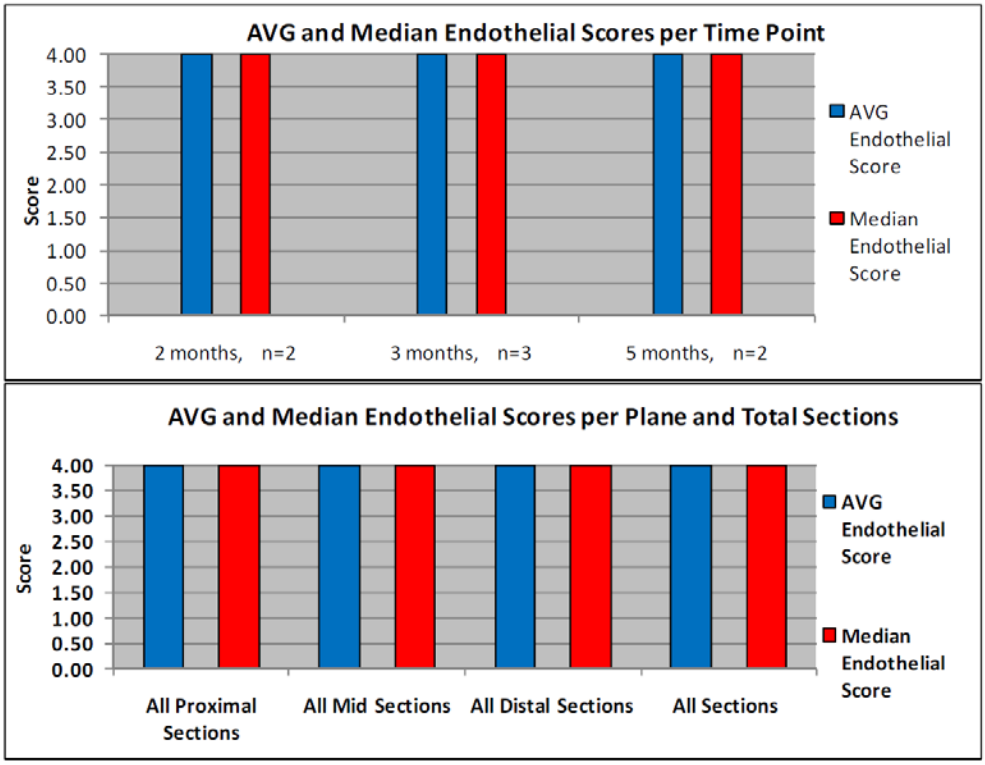


Figure 6. Histopathology assessment of endothelial growth in the pivotal animal trial.

The final report, signed August 14, 2009, stated that cross sections of the treated CS showed optimal local tissue toleration and favorable healing characteristics (fully endothelialized, mature and stable neointima with no residual fibrin). However, photomicrographs provided in a separate final pathology report (signed and dated September 21, 2015) do not show complete endothelialization of the luminal surface of the Reducer, particularly the mid-section of the device. The endothelial score graphs and the veterinary pathologist's conclusion that there was complete endothelialization as early as 57 days is inconsistent with the photomicrographs. Images depict uncovered struts of the mid-section of the implanted Reducer in multiple animals and at all time points (57, 104, and 140 days post-implant). Appendix B Figure 3 of the pathology report dated September 21, 2015 showed uncovered struts of the mid-section of the implanted Reducer in Animal 1082. Uncovered struts are also shown in the submitted microscopic images in Appendix B Figures 2 (Animal 1073), 7 (Animal 1073) and 8 (Animal 1039), and Appendix E Figures 3 (Animal 1035), 9 (Animal 1039), 15 (Animal 1073), 21 (Animal 1082), 22 (Animal 1082), 33 (Animal 1068), and 34 (Animal 1068).

A representative example of incomplete device coverage by an endothelialized neointima is shown in Figure 7.

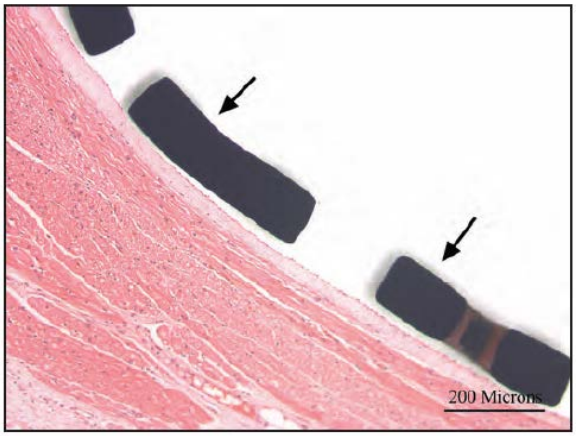


Figure 3. Uncovered struts (in contact with endocardium) (arrows). Animal 1082, Day 104, mid section, (H&E) 10x objective magnification.

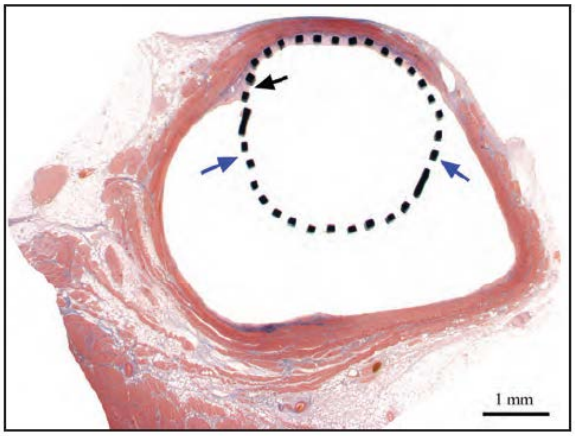


Figure 2. Mallaposed struts within neointima (black arrow); Luminal struts (blue arrows). Animal 1073, Day 104, mid section, (ET) 1.25x objective magnification.

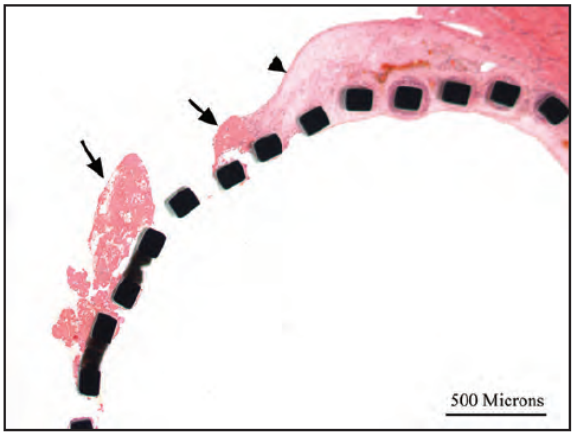


Figure 8. Thrombosis, score 1; Fibrin thrombus (arrows); Organized neointima (arrowhead). Animal 1039, Day 57, mid section, (H&E) 4x objective magnification.

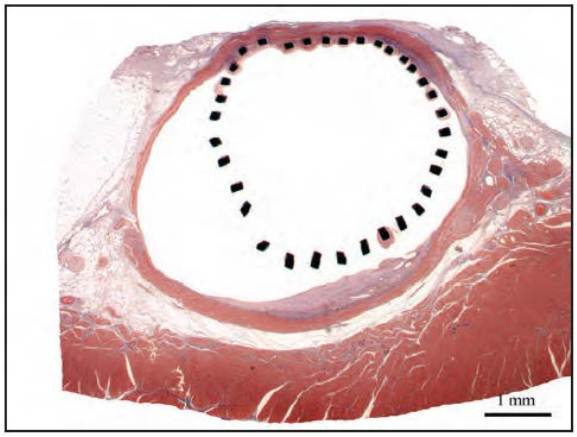


Figure 3. Animal 1035, Day 57, mid section, (ET) 1.25x objective magnification.

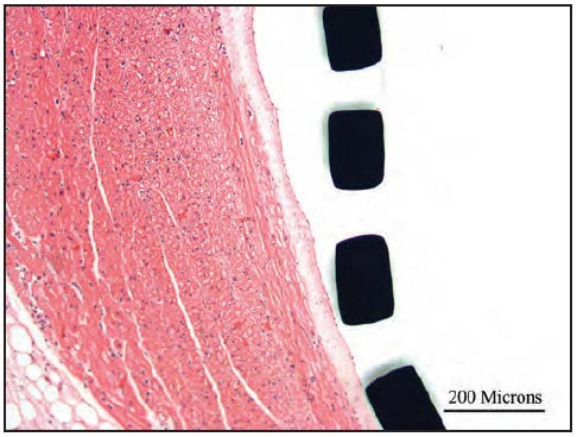


Figure 22. Animal 1082, Day 104, mid section, (H&E) 10x objective magnification.

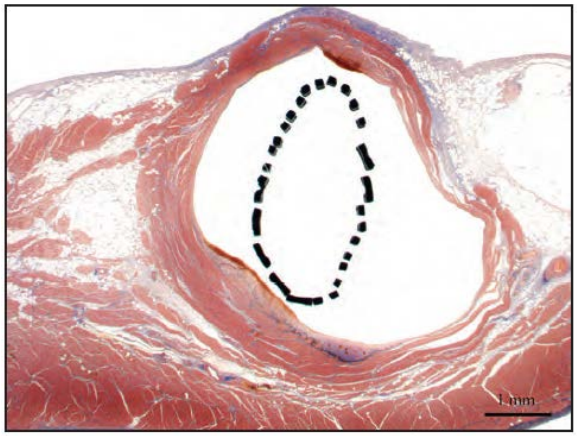


Figure 33. Animal 1068, Day 139, mid section, (ET) 1.25x objective magnification.

Figure 7. Photomicrographs

Micrograph images showing uncovered Reducer struts at late time points challenge the intended ability of the device to restrict CS blood flow through a stenotic central orifice and create a functional CS pressure gradient. Limited animal study data (and clinical data, as discussed subsequently) led FDA to recommend an adjunctive imaging sub-study in humans.

To summarize the limitations of *in vivo* porcine studies:

- There was no imaging data to demonstrate that the Reducer produced a significant CS stenosis.
- Histopathologic and morphometric findings were not adequate to confirm that neointimal proliferation and coverage of the Reducer would be expected to reduce CS blood flow or restrict flow only through the central orifice of the device.
- There are no data demonstrating that the Reducer reproducibly increased CS pressure. In a limited number of animals, the mean trans-Reducer pressure gradient measured 6 months following implantation was only 2.83 ± 1.47 mmHg.
- Reported improvement in left ventricular contractility (by dobutamine stress echocardiography) and myocardial perfusion (by myocardial contrast echocardiography) at 6 weeks and 6 months post-implantation in 4 out of 4 animals in the ischemic Reducer group were not confirmed by FDA's review of the final report raw data.
- Quantitative histomorphometry was performed on Reducer specimens and limited to only 3 transverse sections (proximal, mid, and distal) of the device.
- A visual semi-quantitative estimate of only 2 Reducer CS specimens was provided. In one CS, the proximal and distal narrowing was 15-20% and 10-15%, respectively, at 2.5 months. In the other CS, the proximal and distal narrowing was 55-60% and 25-30%, respectively, at 3.5 months. The core lab pathologist reported that at all time periods, the Reducer was associated with low levels of neointimal proliferation in the coronary sinus.
- Organizing thrombi on the Reducer luminal surface was observed in some animals. Animal lungs were not examined to rule out pulmonary embolism and infarction.
- The veterinary pathologist's comprehensive macroscopic evaluation report of who performed the necropsy of all the animals in the study was not submitted.
- Histologic evaluation of the myocardium, lungs, and other major organs for all animals to identify potential adverse effects in the tissues were not adequately performed or were not performed at all.
- There was no clinical pathological evaluation.
- There were no individual animal medical records and health status reports of all animals before and during the studies, and there was a general lack of raw data for reconstruction of the animal studies.
- The level of quality (attributability, legibility, contemporaneousness, originality, accuracy), integrity, and fitness for use, particularly with respect to use of the animal data for regulatory purposes were deficient since documentation was incomplete, and there were years-long gaps between study conduct and analysis of data.

The sponsor has not provided any additional animal or human clinical data to further address these concerns and have stated that they believe the current collection of animal and human clinical data to be sufficient.

Panel Question: While the animal studies document initial performance of the Reducer device, the data do not demonstrate a consistent neointimal response so as to restrict CS blood flow to the stenotic central portion of the device. FDA is concerned that these data, coupled with the limitations in the clinical data identified in Section 7.4, raise questions regarding the Reducer's effectiveness. If the Panel finds that additional information is needed, they will be asked to discuss and provide guidance on the type of additional data that should be collected (for example, additional animal studies and/or human clinical studies) in order to support a reasonable assurance of safety and effectiveness.

7 Clinical Investigations

This section summarizes the clinical data included in the PMA submission from Neovasc for its Reducer System. FDA presents the trial design, information on study execution, statistical cohorts, and analyses followed by what FDA believes are the most informative analyses to assess the safety and effectiveness of the Neovasc Reducer System. FDA includes comments in each section to point out concepts and information that we believe are important when evaluating study results.

7.1 First in Human (FIH) Study

The FIH study was a 15-patient, open-label, single-arm feasibility study of a first-generation Reducer model (described in Section 3.1.1). The study was conducted from November 2004 to March 2006 at 3 investigational sites in India and Germany. The objective of the study was to evaluate the safety and performance of the Reducer when implanted in patients who demonstrated evidence of reversible ischemia, with an ejection fraction >30%, and who were not candidates for conventional revascularization procedures.

FDA Comment: All candidate subjects were screened and selected by the principal investigator, and the data for potentially eligible subjects were then sent to the sponsor for a final evaluation and determination. The ultimate determination of a subject's eligibility to be included in the FIH study was determined by the medical director for Neovasc.

There were no major procedure-related adverse events during the device implant procedure or during the six-month follow-up period. Major procedure-related adverse events were defined as: death, MI, perforation of the coronary sinus, total occlusion of the coronary sinus, and the need for urgent dilation of the Reducer. There were 3 dislodgments of the Reducer that occurred during the procedure. For two of the cases, the devices were retrieved prior to the implantation of additional devices. In one of these cases, the device migrated from the CS into the pulmonary artery by way of the right atrium into the right ventricle; a decision was made not to attempt retrieval of the device. A second Reducer was then implanted in the CS without complications.

CT angiography showed proper location, lack of migration, and patency of the implanted Reducers at two days and six months post-implantation. Information regarding the presence or absence of CS stenosis or a pressure gradient across the device was not provided. Angina scores

improved in 12 of 14 patients at six months (one patient was excluded from the analysis). The average CCS class was 3.07 ± 0.47 at baseline and 1.64 ± 0.84 at 6 months. Stress-induced ST-segment depression developed in nine patients during the baseline exercise stress test. After six months, stress-induced maximal ST-segment depression was reduced in six of these nine patients from a mean of 1.78 mm at baseline to 1.00 mm at follow up and was eliminated in two of these six patients. The extent and severity of myocardial ischemia by dobutamine echocardiography and by thallium single-photon emission computed tomography was reduced by both methods at six-month follow up.

At 3-years post-implantation, 14 of the 15 FIH Study subjects were evaluated for long-term safety and efficacy of the Reducer. There were no reported deaths, MIs, or adverse events attributed to the device. Three subjects underwent revascularization due to progression of their obstructive CAD. At 3 years, compared to baseline, CCS grade had improved 2 classes in 8 subjects, 1 class in 5 subjects, and was unchanged in 1 subject. CT angiography was conducted on 11 subjects, and the Reducer was reported to be visible, patent, and well positioned, with no evidence of migration. However, a limitation of this study was that the presence or absence of a CS stenosis was not assessed. Table 4 summarizes the three year study results as reported by Banai et al. (2010).

Table 4. Three-year endpoint results from the FIH study

	Baseline (N=15)	6 months (N=15)	3 years (N=14)
CCS class	3.07±0.11	1.73±0.22	1.57±0.23
Dobutamine Echo ischemia severity score (0-2)	1.33±0.28	0.55±0.25	0.45±0.16
Thallium SPECT ischemia severity score (0-2)	1.93±0.06	1.47±0.13	0.82±0.26
Maximal ST segment depression (mm)	1.67±0.33	0.78±0.22	0.67±0.33

A second long-term follow-up evaluation of the FIH patients was conducted in 7 subjects at a single site in India, 12 years post-implantation. CT angiography was performed, and all Reducers were reported to be positioned properly with no migration, occlusion, or thrombosis, and with no visible strut fractures, deformity, or distortions of the device. Measurements performed at the distal, proximal, and middle sections of the device did not show meaningful changes between 6 months and 12 years. The 7 patients reported sustained improvement of angina class compared with baseline status, with 4 patients with at least 2 CCS class angina reduction and 2 patients with at least 1 CCS class reduction.

While informative as a feasibility study, FDA notes several limitations to the data collected in the FIH trial, including:

- The use of a previous version of the device. Differences in device design could affect performance attributes such as patency, flow characteristics, and fracture resistance. The changes to the delivery system could affect device deliverability and procedural success.
- Non-blinded study design such that a placebo effect on subjective symptom improvement cannot be excluded.

- Information on the presence or degree of severity of a CS stenosis or pressure gradient across the device was not assessed, such that no correlations could be made between clinical outcomes and the degree of CS stenosis and CS pressure gradient.
- Stress-induced maximal ST-segment depression and myocardial ischemia (assessed by dobutamine stress echocardiography and thallium scintigraphy) were reduced, but the results are limited by the small sample size, single arm design, missing data, and absence of a correlation with the degree of CS stenosis and CS pressure gradient.
- Lack of an independent clinical events committee.
- Potential selection bias due to the involvement of the sponsor in the inclusion/exclusion evaluation.
- Question regarding whether patients were truly "no option" patients at study initiation (e.g., three patients underwent revascularization due to progression of their coronary artery disease.)

FDA Comment: While the FIH study provided initial basic safety information regarding this treatment approach, the limitations noted above make it challenging for FDA to consider this data beyond an informative initial investigation.

For additional information regarding the FIH Study, please refer to Appendix B.

7.2 Coronary Sinus Reducer for Treatment of Refractory Angina (COSIRA) Trial

Summary: The COSIRA study was a prospective, multicenter, randomized sham-controlled trial conducted at 11 study sites OUS.

A total of 104 out of a planned 124 subjects were enrolled at 11 centers; 52 subjects were randomly assigned to the Reducer treatment group (device arm) and 52 subjects were randomly assigned to the control group (sham procedure). The primary endpoint was the proportion of subjects with an improvement of two or more CCS angina classes from baseline to 6 months post-procedure. The descriptive safety endpoints evaluated technical success, procedural success, differences between treatment groups in periprocedural serious adverse events (SAEs) and major adverse events (MAEs), and a composite of cardiac death, major stroke, and MI.

There was a statistically significant improvement in the primary endpoint of the Reducer group compared to the control (34.6% vs. 15.4%, $p = 0.024$). Regarding safety, the Reducer group showed a 96.2% technical success rate and a 100% procedural success rate. There were 34 serious adverse events (SAEs, 10 Reducer, 24 Control), and the most commonly reported SAEs were unstable angina (2.0% Reducer, 7.4% Control), angina pectoris (2.0% Reducer, 5.6% Control) and chest pain (2.0% Reducer, 5.6% Control).

While the results of this trial were positive, the study had several limitations including: early termination of enrollment, limited sample size, short follow-up period, lack of statistical power to detect improvement in objective parameters of ischemia, no assessment of device-associated creation of a CS stenosis or pressure gradient, and a lack of an assessment of successful subject blinding to treatment assignment.

FDA Comment: The COSIRA trial was conducted outside of the US, and FDA did not provide input into the trial design or conduct. The results from the COSIRA trial were published by Verheye et al. (2015) in the New England Journal of Medicine.

7.2.1 Study Population

The COSIRA population included patients with refractory angina pectoris who demonstrated objective evidence of reversible myocardial ischemia but had limited treatment options and were referred to as "no-option" subjects. In order to be randomized into the COSIRA study, subjects must have fulfilled all of the inclusion and none of the exclusion criteria. Subjects who satisfied all of the inclusion and exclusion criteria but were excluded due to the angiographic criteria were considered to be screen failures.

7.2.1.1 Measurements Assessed

The CCS Angina Grading Scale was used for the classification of severity of angina:

- Class I – Angina only during strenuous or prolonged physical activity
- Class II – Slight limitation, with angina only during vigorous physical activity
- Class III – Symptoms with everyday living activities, i.e., moderate limitation
- Class IV – Inability to perform any activity without angina or angina at rest, i.e., severe limitation

A subject's CCS score was initially determined pre-procedure as part of an in-person assessment with the first follow-up assessment performed at 30 days. At 3 months, the follow-up evaluation was conducted either in person or via telephone based on discussions between the investigator and patient. The final 6-month evaluation was performed in person. For the 12-month evaluation (at the Danish site only), the CCS assessment was conducted by phone or in person based on the investigator's discretion.

The Seattle Angina Questionnaire (SAQ) was used to measure the functional status of subjects in the trial. This assessment was performed pre-procedure as well as 30-days, 3-months, and 6-months post-procedure.

Core laboratories were used to standardize interpretation of data from wall motion score index assessed by DSE, ETT, and CT angiography. Independent reviewers were used for SPECT and MRI data. Adverse events were either reported spontaneously or elicited during questioning and examination of the subject at scheduled follow-up assessments. The severity of adverse events was determined according to the following scale:

- Mild: the patient is aware of a sign or symptom, but it is easily tolerated
- Moderate: discomfort or interference with usual activity
- Severe: incapacitating, with inability to engage in usual activity

Panel Question: As will be discussed in Section 7.2.7, the Panel will be asked to discuss the potential treatment options for these subjects as it pertains to a definable patient population. 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.

7.2.1.2 Eligibility Criteria

7.2.1.2.1 Inclusion Criteria

Subjects could be included in the study only if they met all of the following inclusion criteria.

1) Patient must be older than 18 years of age
2) Symptomatic CAD with chronic refractory angina pectoris classified as Canadian Cardiovascular Society grade III or IV despite attempted optimal medical therapy for 30 days prior to screening
3) Patient has limited treatment options for revascularization by CABG or by PCI
4) Evidence of reversible ischemia that is attributable to the left coronary arterial system by dobutamine echo
5) Left ventricular ejection fraction greater than 25%
6) Male or non-pregnant female (NB: females of child bearing potential must have a negative pregnancy test)
7) Patient understands the nature of the procedure and provides written informed consent prior to enrollment
8) Patient is willing to comply with specified follow-up evaluation and can be contacted by telephone

Prior to December 16, 2011, subjects were required to have ≥ 1 mm ST depression during the ETT in order to meet the inclusion criteria. Neovasc's scientific advisory board (SAB) members, in consultation with investigators, decided that a left bundle branch block (LBBB) should not be exclusionary. Instead, potential COSIRA subjects would need to have a DSE that was positive for ischemia attributed to the left coronary arterial system. At the time of this change, 38 patients had been enrolled with 20 patients randomized to the Reducer group and 18 patients in the Control group).

7.2.1.2.2 Exclusion Criteria

Subjects were excluded from the study for any of the following reasons:

7.2.1.2.2.1 <u>Angiographic</u>

1) Mean right atrial pressure higher than or equal to 15 mmHg
2) Patient with anomalous or abnormal CS as demonstrated by angiogram

Abnormality defined as:

- Abnormal CS anatomy (e.g., tortuosity, aberrant branch, persistent left SVC); and/or
- CS diameter at the site of planned reducer implantation less than 9.5 mm or greater than 13 mm

7.2.1.2.2.2 <u>Clinical & General</u>

3) Recent (within 3 months) acute coronary syndrome
4) Recent (within 6 months) successful PCI or CABG

5) Unstable angina (recent onset angina, crescendo angina, or rest angina with ECG changes) during the 30 days prior to screening
6) Decompensated congestive heart failure (CHF) or hospitalization due to CHF during the months prior to screening
7) Life-threatening rhythm disorders or any rhythm disorders that would require placement of an internal defibrillator and/or pacemaker
8) Severe chronic obstructive pulmonary disease (COPD) as indicated by a forced expiratory volume in one second that is less than 55% of the predicted value
9) Patient cannot undergo exercise tolerance test (bicycle) for reasons other than refractory angina
10) Severe valvular heart disease
11) Patient with pacemaker or defibrillator electrode in the right atrium, right ventricle, or coronary sinus
12) Patient having undergone tricuspid valve replacement or repair
13) Chronic renal failure (serum creatinine >2 mg/dL), including patients on chronic hemodialysis
14) Moribund patients, or patients with comorbidities limiting life expectancy to less than one year
15) Contraindication to required study medications that cannot be adequately controlled with pre-medication
16) Known allergy to stainless steel or nickel
17) Contraindication to having an MRI performed (NB: cardiac MRI subset patients only)
18) Currently enrolled in another investigational device or drug trial that has not completed the primary endpoint or that clinically interferes with the current study endpoints

7.2.2 Study Design

COSIRA was a prospective, multicenter, randomized, double-blind, sham-controlled (1:1 randomization ratio) study of the safety and effectiveness of the Reducer. COSIRA subjects were blinded to the treatment group to which they were assigned. Independent, blinded physicians performed the pre- and post-procedural CCS assessments and Seattle Angina Questionnaires. Dobutamine stress echo and exercise tolerance test (ETT) core laboratories and physicians performing the independent analysis of the SPECT and MRI results were also blinded to group assignments.

7.2.2.1 Study Blinding and the Sham Control

Following enrollment, all prospective study subjects underwent screening tests to determine eligibility. Measurement of right atrial pressure and coronary sinus angiography were the final screening tests, following which eligible subjects were randomized to either the Control or Reducer group. In the subjects randomized to the Control group, the procedure was completed following the right atrial pressure measurement and coronary sinus angiography, thus making this the sham-control (Control) procedure. Subjects randomized to the Reducer group had a device implanted immediately following the coronary sinus angiography. All subjects remained unaware of their study assignment throughout the study period (i.e., 6 months).

To maintain subject blinding, the implanting physicians were instructed to behave in the same manner with both Control and Reducer group patients. When possible, subjects were given headphones with music so that they could not hear discussions between the physician and medical staff. Subjects were draped for the procedure in a way that they could not see the procedural monitors, and subjects and their families were told that the length of the procedure was not indicative of whether or not they underwent an implantation of the Reducer.

The Sponsor was not blinded to the treatment arm for each subject, as the Sponsor was present during all implantations.

Panel Question: 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 they believed they were assigned. A notable placebo effect was observed in the COSIRA control group, which presents challenges for interpreting the data given the limited sample size. The Panel will be asked to discuss the robustness of the trial results given the lack of a blinding assessment and limited sample size. The Panel will also be asked to discuss and make recommendations regarding the need for additional clinical data in view of a lack of a blinding assessment.

7.2.2.2 Randomization

A total of 104 subjects were randomized in a 1:1 ratio using a computer-generated permuted block randomization scheme with investigational sites as strata. Fifty-two subjects were randomized to the Control group and did not receive an investigational device, and 52 subjects were randomized to the Reducer group.

All subjects enrolled and randomized in the COSIRA study, if not already taking aspirin and clopidogrel or prasugrel, were placed on these medications for the duration of the clinical study (6 months follow up) unless contraindicated. Subjects who were randomized to the Reducer group received heparin or bivalirudin once randomized and prior to the Reducer implantation unless contraindicated.

7.2.3 Primary and Secondary Analyses

7.2.3.1 Primary Effectiveness Endpoint

The prespecified primary effectiveness endpoint for the COSIRA study was the proportion of subjects with an improvement of two or more CCS angina classes from baseline to 6 months after the procedure using an intention-to-treat (ITT) analysis as defined in Section 7.2.4.1.

7.2.3.2 Descriptive Safety Endpoints

A primary safety endpoint was not prospectively defined for this trial. However, the protocol identified multiple secondary safety endpoints that the sponsor has chosen to evaluate the safety of the Reducer device. The COSIRA study safety endpoints were defined as:

- Technical Success in the Reducer group, defined as successful delivery and deployment of the Reducer to the intended site as assessed by the investigator.
- Procedural Success in the Reducer group, defined as technical success and the absence of acute need for clinically-driven intervention to address an Adverse or Serious Adverse Device Effect prior to hospital discharge, as adjudicated by the Clinical Events Committee (CEC).
- Periprocedural SAE in the Reducer group, defined as a composite of death, MI, cardiac tamponade, clinically-driven re-dilation of a failed Reducer, life-threatening arrhythmias (ventricular tachycardia (VT) or ventricular fibrillation (VF)), and respiratory failure through 30 days post-procedure, as adjudicated by the CEC.
- Periprocedural SAE in the Control group, defined as a composite of death, MI, cardiac tamponade, life-threatening arrhythmias (VT or VF), and respiratory failure through 30 days post-procedure, as adjudicated by the CEC.
- MAEs: a composite of cardiac death, major stroke, and MI in the Reducer and Control groups through hospital discharge, and at 30-day, 3-month, and 6-month post-procedural evaluations.

Panel Question: Angina can be a placebo-responsive condition. For this reason, the ETT has been used as an objective measure of functional capacity and as a predicable threshold of ischemia, and therefore has been considered acceptable as a primary endpoint in clinical trials that have evaluated anti-ischemic treatments. The Panel will be asked to discuss and comment on the subjective assessment of angina as a clinically meaningful correlate of ischemia for the primary endpoint for the COSIRA trial.

7.2.3.3 Secondary Effectiveness

Secondary efficacy endpoints assessed in the Reducer and Control groups included:

- CCS Classification: The proportion of patients with an improvement of one or more CCS classes from baseline to 6 months post-procedure.
- DSE Wall Motion Score Index (WMSI) at baseline and 6-month post-procedure.
- SAQ Score at baseline and 6-month post-procedure.
- Total Exercise Duration, Time to 1 mm ST Segment Depression, Maximal ST Segment Depression, Metabolic Equivalents of Task (METs), and Double Product by Exercise Tolerance Test at baseline and 6-month post-procedure.

Panel Question: While not included as part of the primary analysis, an objective measure of ischemia was assessed as part of the secondary analysis in the form of ETT. However, as will be discussed in Section 7.3.4.5, there were large amounts of missing information. The Panel will be asked to comment on overall device effectiveness observed in the COSIRA trial, considering the small sample size, high control group response rate, significant amounts of missing data for objective assessments, and lack of a prespecified hypothesis test for an objective assessment of an improvement in myocardial ischemia.

7.2.3.4 Observational Measures

Observational measures included:

- Thallium/methoxyisobutylisonitrile (MIBI) SPECT Segmental Analysis in the Reducer and Control groups at baseline and 6-months post-procedure.
- CT Angio Analysis in the Reducer patients only at 6-months post-procedure.
- Cardiac MRI Endocardial/Epicardial Blood Flow Distribution and Wall Motion Analysis in the subset Reducer and Control group undergoing perfusion cardiac MRI at baseline and 6-months post-procedure.

7.2.4 Statistical Methodology

Primary effectiveness endpoint analysis:

H_0: Proportion of patients in the Reducer group with a decrease of 2 or more CCS grades at 6 months = Proportion of patients in the Control group with a decrease of 2 or more CCS grades at 6 months

Vs.

H_1: Proportion of patients in the Reducer group with a decrease of 2 or more CCS grades at 6 months ≠ Proportion of patients in the Control group with a decrease of 2 or more CCS grades at 6 months

The protocol specified that the difference between the group proportions was to be calculated and compared with the Pearson chi-square test with continuity correction. However, for the primary endpoint analysis (both ITT and per-protocol (PP)), the Pearson chi-square test without continuity correction was used; the expected values were all greater than 5, so the continuity correction was determined by the sponsor to not be necessary.

Safety endpoints analysis: The safety endpoints are descriptive only and are composed of endpoints included in the secondary endpoint analysis. There was no pre-specified statistical hypothesis for the safety endpoints.

Secondary endpoint analysis: There was no pre-specified statistical hypothesis for any of the secondary endpoints.

Whenever appropriate, the mean, standard deviation (SD), and median are presented for continuous variables, whereas the frequencies and percentage were calculated for categorical variables.

One interim analysis was planned after 50% of the cohort (62 of the intended 124 subjects) completed their 6-month follow-up visit. The results of the interim efficacy assessment were to be based on the Lan-DeMets method using an O'Brien-Fleming spending function ($p<0.0031$). The p-value threshold for the final primary endpoint ITT analysis was set at 0.0469 (instead of 0.05), due to the interim analysis that was performed.

Panel Question: The sponsor provided a statistical hypothesis for the primary effectiveness endpoint. However, there was no pre-specified statistical hypothesis for the safety endpoints, and the safety endpoint event rates are presented descriptively. Given that the subject device is a permanent implant, and that patients with angina may be young (one enrolled subject was 35 years of age) with a low overall rate of mortality, the Panel will be asked to discuss and make recommendations on the need for a pre-specified, statistically powered hypothesis to support a reasonable assurance of safety.

Additionally, while the sponsor has collected longer-term data on an earlier version of the device in a limited number of subjects, the COSIRA trial followed subjects for only 6 months. Adjunctive information regarding long-term data utilizing the current device design has been collected as part of the REDUCER-I study (Section 7.5); however, this data includes additional imitations. The Panel will also be asked to discuss and make recommendations on the need for additional premarket longer term data to support a reasonable assurance of safety and effectiveness.

7.2.4.1 Analysis Populations

Analysis populations were defined as the following:

- *Intent-to-treat (ITT) population:* included all randomized subjects and consists of all subjects who signed the written informed consent, were considered to meet the study entry criteria, and were randomized to a study group. Each subject was analyzed according to his or her original randomized treatment group. The ITT population consisted of 104 subjects: 52 in the Reducer group and 52 in the Control group.
- *Per-protocol (PP) population:* included only subjects who completed the study per the study protocol. Subjects who did not complete the study or were randomized to the Reducer group but did not receive a device due to technical failure were not analyzed in the per-protocol group. The PP population consisted of 102 subjects: 50 in the Reducer group and 52 in the Control group. Subjects (b) (6) and (b) (6) were randomized to the Reducer group but did not have the Reducer implanted.
- *As Treated (AT) population:* was limited to those that did not have a Reducer implanted but were still blinded. These subjects were added to the Control group in the "as-treated" analysis. The AT population consisted of 104 subjects according to the actual treatment received: 50 in the Reducer group and 54 in the Control group. Subjects (b) (6) and (b) (6) were moved from the Reducer group to the Control group in the As-Treated population.
- *Safety population:* included all randomized subjects. All safety analyses evaluated subjects according to the actual treatment received, and were performed using the safety population, which is equivalent to the AT population.

7.2.4.2 Handling of Missing Information

While CCS class was recorded for all subjects, imputation for missing secondary data was performed using the last observation carried forward (LOCF) method, along with a multiple imputation method and tipping point analysis.

7.2.4.3 Changes in the Planned Analyses

Several subgroup analyses specified in the statistical analysis plan (SAP) were not performed:

- Location of the myocardial ischemia with respect to the placement of the Reducer: this analysis was not possible as angiographic imaging was not performed in such a way as to clearly show drainage of the coronary arteries into the coronary sinus. As this was not done, angiographic analysis could not be performed to determine location of the Reducer in the coronary sinus with respect to the area of reversible ischemia.
- The total ischemic burden analyses were not possible because the sponsor stated that this measure was not captured in a useful manner for statistical analysis. Additional explanation regarding the lack of total ischemic burden analyses was not provided.

7.2.5 Sample Size

The sample size calculation was based on the following assumptions:

- H_0: Proportion of patients in the Reducer group with a decrease of 2 or more CCS grades at 6 months = Proportion of patients in the Control group with a decrease of 2 or more CCS grades at 6 months
- H_1: Proportion of patients in the Reducer group with a decrease of 2 or more CCS grades at 6 months ≠ Proportion of patients in the Control group with a decrease of 2 or more CCS grades at 6 months
- Based on a literature review, the proportion of patients expected to exhibit an improvement of 2 or more CCS grades at 6 months is 0.40 (Reducer) and 0.15 (Control)
- Type I error rate of 5% (2-sided)
- Power of 80%
- Calculation based on the Pearson chi-square test with continuity correction

Based on these assumptions, the sample size was 56 subjects per group (a total of 112 subjects). It was further assumed that up to 10% of the randomized cohort may not complete the six-month evaluations. The sample size was therefore increased to a maximum of 62 per group, for a total trial size of 124. However, based on a difficulty enrolling subjects, the sponsor elected to halt enrollment in the study with a total of 104 subjects.

7.2.6 Follow Up Schedule

Subjects in the COSIRA trial were scheduled for follow-up visits at 30 days, 3 months, and 6 months post-procedure. Follow-up visits consisted of a review of medical history, including adverse events (AEs), a bicycle symptom-limited stress test, DSE, SPECT radionuclide perfusion testing, trans thoracic echo, stress echo, perfusion MRI, CCS assessment, Seattle Angina Questionnaire, and a 12-lead ECG. The Swedish site (08) and Danish site (05) originally planned to conduct 12-month follow-up visits. However, after the Reducer received a CE, the Swedish site determined that these visits were no longer required.

7.2.7 Subject Characteristics

7.2.7.1 Subject Accountability

There was a total of 166 subjects screened leading to 104 subjects enrolled and randomized in the COSIRA study. There were 62 screening failures. Table 5 summarizes the screen failures, and Figure 8 is a study flow diagram.

Table 5. Screening Failures

Screening Failure Reason	Number of Screening Failures N=62
Coronary sinus too large (angiographic screening)	3 (4.8%)
Physician's decision	3 (4.8%)
Negative stress test (ETT)	3 (4.8%)
Revascularization possible	1 (1.6%)
Adverse event during screening test	2 (3.2%)
CCS classification I–II	1 (1.6%)
Severe COPD	1 (1.6%)
Pacemaker present	1 (1.6%)
No ischemia	1 (1.6%)
Negative DSE	36 (58.1%)
Normal SPECT	1 (1.6%)
Withdrew consent prior to procedure	5 (8.1%)
Enrollment stopped during screening	2 (3.2%)
Unknown reason	2 (3.2%)

Figure 8 illustrates the COSIRA Study Flow.

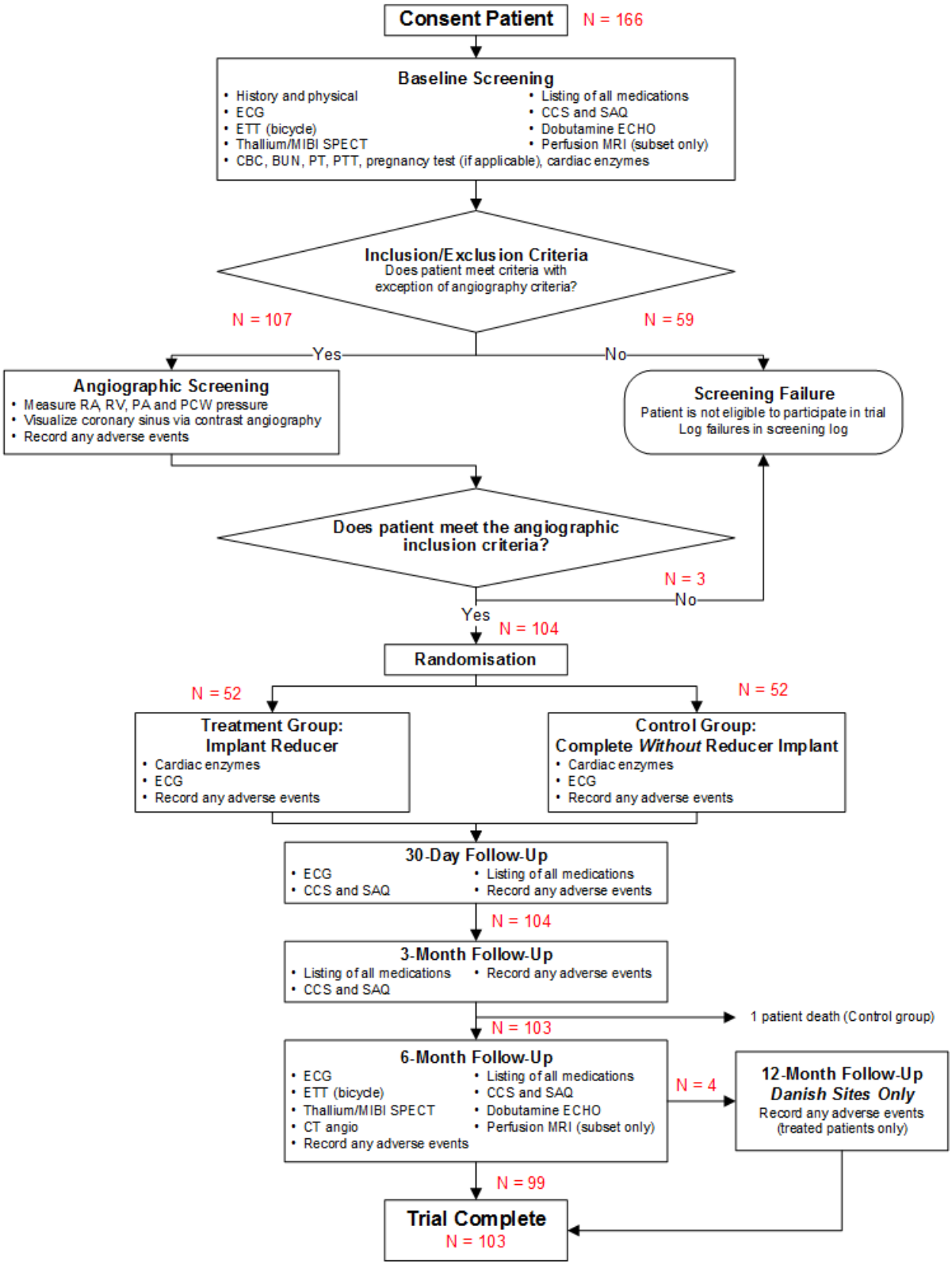


Figure 8. COSIRA Study Flow Chart

7.2.7.2 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics were similar between treatment groups (Table 6). 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.

Table 6. 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

FDA Comment: As noted from the data provided in Table 6, the COSIRA study demographics were not representative of the US CAD population. Specifically, no black or Hispanic subjects were enrolled, and female subjects represented only 19.2% of the study enrollment.

Previous medical history is summarized in Table 7. The Reducer group had numerically fewer diabetics (40.4% vs. 48.1%), but the two groups were comparable with regard to smoking history, hypercholesterolemia, hypertension, family history of cardiovascular disease, and other relevant medical history. Of the 104 subjects, 73.1% had a history of PCI, 76.9% had a history of CABG, and 54.8% had a history of MI.

Table 7. Baseline Medical History and Baseline Cardiovascular Tests

	Reducer N=52	Control N=52
Medical History – n (%)		
Diabetes mellitus		
Yes	21 (40.4)	25 (48.1)
If yes, treated with insulin	8 (15.4)	14 (26.9)
If yes, treated with (oral) hypoglycemics	12 (23.1)	11 (21.2)
If yes, treated with exercise/diet alone	1 (1.9)	0 (0)
Smoking of cigarettes		
Previous smoker	22 (42.3)	24 (46.2)

	Reducer N=52	Control N=52
Never smoked	25 (48.1)	21 (40.4)
Current smoker	5 (9.6)	7 (13.5)
Hypercholesterolemia		
Yes	50 (96.2)	46 (88.5)
If yes, requiring medication	49 (94.2)	42 (80.8)
If yes, not requiring medication	1 (1.9)	4 (7.7)
Hypertension		
Yes	42 (80.8)	41 (78.8)
If yes, requiring medication	42 (78.8)	41 (80.8)
If yes, not requiring medication	0 (0)	0 (0)
Family history of cardiovascular diseases		
Yes	39 (75.0)	37 (71.2)
No	7 (13.5)	9 (17.3)
Unknown	6 (11.5)	6 (11.5)
Valve disease	2 (3.8)	4 (7.7)
Present or recurrent arrhythmias	10 (19.2)	12 (23.1)
Congestive heart failure	1 (1.9)	2 (3.8)
Other vascular diseases		
Yes	6 (11.5)	9 (17.3)
Peripheral vascular disease	6 (11.5)	8 (15.4)
Previous stroke	1 (1.9)	4 (7.7)
Previous MI		
Yes	27 (51.9)	30 (57.7)
If yes, Q-Wave	11 (21.2)	6 (11.5)
If yes, non-Q-Wave	10 (19.2)	14 (26.9)
Previous PCI	36 (69.2)	40 (76.9)
Previous CABG	42 (80.8)	38 (73.1)
Dobutamine ECHO		
Performed – n (%)	50 (96.2)	50 (96.2)
Positive for reversible ischemia – n (%)	44 (88.0)	47 (94.0)
Wall motion abnormalities at rest – n (%)	29 (58.0)	30 (60.0)
Valve dysfunction at rest – n (%)	1 (2.0)	4 (8.0)
LVEF		
Performed – n (%)	47 (90.4)	46 (88.5)
Ejection fraction (%)		
N	47	44
Mean	53.5	54.75
Standard deviation	10.2	11.9
Median	55	58
IQR	45–60	47.75–65
Min – Max	33–74	30–83
SPECT		
Performed – n (%)	51 (98.1)	48 (92.3)

	Reducer N=52	Control N=52
N with Thallium or MIBI specified	48	45
Thallium – n (%)	6 (12.5)	7 (15.6)
MIBI – n (%)	42 (87.5)	38 (84.4)
Positive for reversible ischemia – n (%)	44 (86.3)	37 (77.1)
Irreversible perfusion defects detected – n (%)	18 (35.3)	14 (29.2)

A summary of the number of antianginal medications at enrollment is provided in Table 10. The majority of subjects were taking at least one antianginal medication (93.3%), while 36.5% were taking 3 or more. Also, ≥25% of subjects were on 0 or 1 antianginal medication, which is notable in a refractory angina population.

Table 8. 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.

Baseline cardiovascular medications, taken within 30 days prior to the procedure, are summarized in Table 8. All subjects in both groups were taking cardiovascular medications as directed in the protocol; most subjects (92.3%) were taking ASA/aspirin (anti-platelets), and/or ß-blocker (76.9%), and/or statins (89.4%). No justification was provided regarding the proportion of patients prescribed ß-blockers, nitrates, and Ca^+ blockers in a refractory angina population. Additionally, no information was provided about medication compliance, or whether patients were on therapeutic or maximally tolerated doses.

Table 9. Cardiovascular Medications at Screening

Baseline Cardiovascular Medications – n (%)	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)
Ca^+ 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)

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

Table 10. Baseline SAQ Scores

SAQ Scores: Physical Limitation	Reducer N=48	Control N=44
Mean	47.9	44.7
Standard deviation	24.4	24.1
Median	50.0	38.9
IQR	30.6–63.2	28.5–63.2
Min – Max	8.3–94.4	8.3–94.4
Anginal Stability	**N=49**	**N=45**
Mean	42.9	38.3
Standard deviation	22.6	26.1
Median	50.0	50.0
IQR	25.0–50.0	25.0–50.0
Min – Max	0–100.0	0–100.0
Anginal Frequency	**N=49**	**N=45**
Mean	42.9	47.3
Standard deviation	24.8	28.4
Median	40.0	40.0
IQR	20.0–60.0	20.0–70.0
Min – Max	0–90.0	0–100.0
Treatment Satisfaction	**N=49**	**N=45**
Mean	79.7	78.0
Standard deviation	18.3	18.2
Median	81.3	81.3
IQR	68.8–96.9	65.6–92.7
Min – Max	25.0–100.0	25.0–100.0
Quality of Life	**N=49**	**N=45**
Mean	42.4	45.9
Standard deviation	19.8	20.7
Median	41.7	41.7
IQR	33.3–58.3	29.2–62.5
Min – Max	0–83.3	16.7–100.0

Table generated by FDA.

The baseline CCS scores are summarized in Table 11. A CCS score of 3 or greater was required for subjects to be included in the COSIRA study.

Table 11. Baseline CCS Scores

Baseline CCS Scores – n (%)	Reducer N=52	Control N=52
CCS Class 3	42 (80.8)	45 (86.5)
CCS Class 4	10 (19.2)	7 (13.5)

7.3 COSIRA Study Results and Analyses

7.3.1 Interim Analysis for Effectiveness

An interim analysis was performed for the primary effectiveness endpoint (reduction in 2 or more CCS classes from baseline to 6 months) after 50% of the cohort (62 of the intended 124 subjects) completed their 6-month follow-up visit. In the interim report dated January 25, 2013, the sponsor indicated that using Pearson's chi-squared test with Yates's continuity correction, a p-value of 1.00 was found. Because a statistically significant difference at the $\alpha = 0.0031$ level was not observed, the trial was not stopped. In accordance with the clinical protocol, at the time of the interim analysis, the Data Safety Monitoring Board (DSMB) evaluated the primary endpoint outcome along with the conditional power for futility, which was reported to be 27.2%.

Upon FDA's request for additional information regarding the interim study results, it was communicated that the original interim analysis report had been compiled by a clinical research organization (CRO) used to collect and organize the COSIRA study data. The sponsor indicated that this CRO was no longer under contract with the sponsor, no longer had any records related to the study, and therefore would be unable to provide any additional information or analyses. In light of this, the sponsor provided their own reanalysis of the data, and reported a p-value of 0.129 (Pearson's chi-squared test with Yate's continuity correction) and a p value of 0.068 (Pearson's chi-squared test without continuity correction) for the interim analysis of 62 subjects. However, because it was unclear how the initial interim analysis was performed and which subjects were included in these reanalyses, FDA was unable to verify these calculations or address the discordant results between the original CRO interim analysis and the sponsor's subsequent interim analysis.

7.3.2 Effectiveness Results and Analyses

7.3.2.1 Primary Effectiveness Endpoint

As specified in the COSIRA study protocol, the primary effectiveness endpoint was defined as an improvement of two or more CCS grades from baseline to 6-months post-procedure in the Reducer group in the ITT population. In the Reducer group, 18/52 subjects (34.6%) experienced a decrease in two or more CCS grades from baseline to 6 months vs. 8/52 subjects (15.4%) in the Control group ($p = 0.024$, see Table 12 – Table 14).

Table 12. Primary Endpoint Analysis – Intent-to-Treat

CCS Score – n (%)	Reducer N=52 (95% CI)	Control N=52 (95% CI)
≥ 2 Class CCS improvement	18 (34.6) (21.7, 47.5)	8 (15.4) (5.6, 25.2)
Pearson's chi-squared test = 5.128 with 1° freedom p = 0.024		

Table 13. COSIRA CCS Scores at 6-Month Follow-Up

CCS Score – n (%)	Reducer N=52	Control N=52
CCS Class 1	16 (30.8)	5 (9.6)
CCS Class 2	18 (34.6)	11 (21.1)
CCS Class 3	13 (25.0)	26 (50.0)
CCS Class 4	5 (9.6)	7 (13.5)

Table 14. COSIRA CCS Analysis – Intent-to-Treat

CCS Analysis	Reducer	Control
Baseline	**N=52**	**N=52**
Mean	3.19	3.13
Standard deviation	0.40	0.35
Min – Max	3 – 4	3 – 4
6-month follow-up (6MFU)	**N=52**	**N=51**
Mean	2.13	2.61
Standard deviation	0.97	0.98
Min – Max	1 – 4	0 – 4
Δ in CCS (Baseline to 6MFU)	**N=52**	**N=51**
Mean	1.06	0.53
Standard deviation	0.94	0.97
Min – Max	-1 – 3	-1 – 3

<u>Panel Question:</u> For the primary effectiveness analysis, 34.6% of subjects treated with the Reducer device demonstrated success, while 15.4% of the sham control group demonstrated success. Additionally, while 34.6% of the Reducer group demonstrated success, 65.4% (34/52) did not. The Panel will be asked to discuss and make recommendations on the primary effectiveness rate associated with Reducer device implantation. The Panel will also be asked to consider whether additional premarket data are needed to confirm these results given the primary effectiveness rate compared to the control, the relatively modest responder rate for a permanently implanted device, and the uncertain durability of these results (since RCT data was only collected to 6-months post-procedure).

7.3.2.1.1 Primary Endpoint – Per-Protocol Analysis

The per-protocol analysis for the primary endpoint excluded 2 of 52 subjects who were randomized to the Reducer group but were not successfully implanted. In the Reducer group, 18/50 subjects (36.0%) experienced a decrease of two or more CCS grades from baseline to 6 months. In the Control group, 8/52 subjects (15.4%) had a decrease of two or more CCS grades from baseline to 6 months. This difference was statistically significant (p = 0.017, Table 18).

Table 15. Primary Endpoint Analysis – Per-Protocol

CCS Score – n (%)	Reducer N=50	Control N=52
≥ 2 Class CCS improvement	18 (36.0)	8 (15.4)
Pearson chi-squared test = 5.704 with 1° freedom p = 0.017		

7.3.2.1.2 Primary Endpoint Analysis – As-Treated

In the AT analysis, two subjects randomized into the Reducer group did not have a Reducer implanted (subjects (b) (6) and (b) (6)). In the Reducer group, 18/50 subjects (36.0%) experienced a decrease of two or more CCS grades from baseline to 6 months. For the Control group, this was experienced by 8/54 subjects (14.8%). This difference was statistically significant (p = 0.013, Table 16).

Table 16. Primary Endpoint Analysis – As-Treated

CCS Score – n (%)	Reducer N=50	Control N=54
≥ 2 Class CCS improvement	18 (36.0)	8 (14.8)
Pearson chi-squared test = 6.214 with 1° freedom p = 0.013		

7.3.3 Safety Results and Analysis

Safety data were collected through 6 months, except for the Danish site, which was required by the protocol to follow subjects for 12 months (n=4). All analyses were performed using the AT population (i.e., subjects that received the device, n=50) except for technical success, which used the ITT population (n=52). Only one subject did not complete the trial: a control subject (b) (6) died of multi-system failure on Day 118.

7.3.3.1 Technical Success

Technical success was assessed in the Reducer group and defined as successful delivery and deployment of the Reducer to the intended site as assessed by the investigator. In the 52 subjects who were randomized to the Reducer group, 50/52 (96.2%) had a Reducer successfully implanted. In both instances where there was a technical failure, the failure to implant the Reducer was due to anatomical variations (e.g., an inability to advance the guide catheter over the guidewire) and not due to device design and/or performance.

Table 17. Technical Success

Technical Success – n (%)	Reducer Group N=52
Subjects successfully implanted with the Reducer	50 (96.2)
Subjects randomized to receive Reducer who did not receive it	2 (3.8)

7.3.3.2 Procedural Success

Procedural success was assessed in the Reducer group and defined as technical success and the absence of acute need for clinically-driven intervention to address an Adverse or Serious Adverse Device Effect prior to hospital discharge, as adjudicated by the CEC. As stated in Section 7.3.3.1, there were two technical failures in which Reducers could not be implanted in 2 of the 52 subjects randomized to the Reducer group. Of the 50 subjects who were successfully implanted with the Reducer, 50/50 (100%) were considered to be a procedural success.

7.3.3.3 Adverse Events

In COSIRA, 66.3% of subjects experienced at least one AE (64.0% Reducer, 68.5% Control). Overall, there were 169 AEs reported (76 Reducer, 93 Control). There were two periprocedural SAEs that both occurred in one Reducer subject (b) (6) : an MI shortly after discharge and again 27 days after the procedure. There was one death (multiorgan failure at day 118) in the Control group, and 34 SAEs (12.0% Reducer, 20.4% Control). There were 5 Major Adverse Events (MAEs) occurring in one Reducer subject and four Control subjects (MAE is defined in Section 10.2.4). There was one MI in the Reducer group, and 3 MIs and a cardiac death in the Control group.

Additional information regarding the timing of post-procedure adverse events and adverse event severity can be found in Appendix A.

7.3.3.4 Related Adverse Events (Table 18)

The majority of the AEs were judged to be not related to the index procedure (92.3%) or the investigational product (95.9%). There were 7 events that were considered related or probably related to the index procedure (5 Reducer, 2 Control). Events in the Reducer group included puncture site bleeding, chest pain, unstable angina, arrhythmia, and gastrointestinal bleeding. Events in the Control group included elevation of troponin and bleeding at the puncture site.

There were 3 events considered related or probably related to the investigational product. All 3 events occurred in the Reducer group as expected, since there is no investigational product in the Control group. The events were the same – unstable angina, arrhythmia and gastrointestinal bleeding – as those considered related to the index procedure.

Table 18. Adverse Events Relatedness

By Number of Events	Reducer N=76	Control N=93
Relationship to Index Procedure		
Not related – n (%)	68 (89.5)	88 (94.6)

By Number of Events	Reducer N=76	Control N=93
Unlikely – n (%)	3 (3.9)	3 (3.2)
Probably related – n (%)*	2 (2.6)	0 (0)
Related – n (%)	3 (3.9)	2 (2.2)
Relationship to Investigational Product		
Not related – n (%)	69 (90.8)	92 (98.9)
Unlikely – n (%)	4 (5.3)	1 (1.1)
Probably related – n (%)*	1 (1.3)	0 (0)
Related – n (%)	2 (2.6)	0 (0)

* Or "possibly related", according to the CEC, for subject (b) (6).

7.3.3.5 Deaths, Other Serious Events and Other Significant Adverse Events

7.3.3.5.1 Deaths

The only death occurred in the control group; this subject died of multi-organ failure on Day 118. The death was adjudicated by the CEC as not related to the sham procedure.

7.3.3.5.2 Other Serious Adverse Events (Table 19)

There were 34 SAEs in total (10 Reducer, 24 Control) in 17 subjects (6 Reducer, 11 Control). The majority of the SAEs were categorized as cardiac disorders, as would be expected for this subject population. Overall, fewer Reducer subjects (12.0%) experienced an SAE than Control (20.0%). The mostly commonly reported SAEs were unstable angina (2.0% Reducer, 7.4% Control), angina pectoris (2.0% Reducer, 5.6% Control) and chest pain (2.0% Reducer, 5.6% Control).

Table 19. Serious Adverse Events – by Subject

MedDRA System Organ Class	Reducer	Control
Preferred term	N=50	N=54
Any Serious Adverse Event	**6 (12.0)**	**11 (20.4)**
Cardiac disorders	**3 (6.0)**	**8 (14.8)**
Acute coronary syndrome	0 (0)	2 (3.7)
Acute myocardial infarction	1 (2.0)	0 (0)
Angina pectoris	1 (2.0)	3 (5.6)
Angina unstable	1 (2.0)	4 (7.4)
Arrhythmia	0 (0)	1 (1.9)
Cardiac failure chronic	1 (2.0)	0 (0)
Myocardial infarction	1 (2.0)	1 (1.9)
Gastrointestinal disorders	**1 (2.0)**	**1 (1.9)**
Abdominal pain upper	0 (0)	1 (1.9)
Crohn's disease	1 (2.0)	0 (0)
Gastrointestinal hemorrhage	1 (2.0)	0 (0)
General disorders and administration site conditions	**1 (2.0)**	**4 (7.4)**
Chest pain	1 (2.0)	3 (5.6)
Multi-organ failure	0 (0)	1 (1.9)

MedDRA System Organ Class	Reducer	Control
Injury, poisoning and procedural complications	**1 (2.0)**	**0 (0)**
Laceration	1 (2.0)	0 (0)
Respiratory, thoracic and mediastinal disorders	**1 (2.0)**	**3 (5.6)**
Chronic obstructive pulmonary disease	1 (2.0)	1 (1.9)
Cough	0 (0)	1 (1.9)
Pulmonary edema	0 (0)	1 (1.9)

Additional information regarding Periprocedural Events and MAEs can be found in Appendix A.

7.3.4 Secondary Endpoints

7.3.4.1 Secondary Effectiveness CCS Endpoint

The secondary CCS endpoint was an improvement of one or more CCS grades from baseline to 6-months post-procedural evaluation in the Reducer group. A success was defined as a subject who had a reduction of at least one grade in CCS classification from the baseline screening to the 6-month post-procedural evaluation.

The proportion of subjects experiencing an improvement of one or more CCS classes from baseline to 6 months in the ITT population was 37/52 (71.2%) in the Reducer group compared with 22/52 (42.3%) in the Control group. The secondary CCS endpoint was also analyzed for the PP population as defined in Section 7.2.4.1. The proportion of subjects experiencing an improvement of one or more CCS classes from baseline to 6 months was 36/50 (72.0%) in the Reducer group compared with 22/52 (42.3%) in the Control group. Additionally, the secondary CCS endpoint was analyzed for the AT population with the number of subjects experiencing an improvement of one or more CCS classes from baseline to 6 months being 36/50 (72.0%) in the Reducer group compared with 23/54 (42.6%) in the Control group (Table 20).

Table 20. Secondary CCS Endpoint Analysis

CCS Score (ITT) – n (%)	Reducer N=52	Control N=52
≥1 Class CCS improvement	37 (71.2)	22 (42.3)
CCS Score (PP) – n (%)	**N=50**	**N=52**
≥1 Class CCS improvement	36 (72.0)	22 (42.3)
CCS Score (AT) – n (%)	**N=50**	**N=54**
≥1 Class CCS improvement	36 (72.0)	23 (42.6)

7.3.4.1.1 Individual Changes in CCS Grade

Based on the data provided in the PMA submission, FDA performed an analysis of the individual changes in CCS Grades. Table 21 provides an overview of the changes in CCS grade based on classification at enrollment. This table illustrates that although a proportion of subjects had an improvement in CCS grade as noted by the primary and secondary effectiveness endpoints, some subjects reported either no change (13/52, 25.0% vs. 24/51, 47.1% for the Reducer and Control group, respectively), or an increased CCS grade at 6 months (2/52, 3.8% vs. 5/51, 9.8%,

respectively). It should be noted that one subject in the Control group died prior to the 6-month follow-up assessment and was therefore excluded from this analysis.

When considering subjects enrolled with CCS grade IV angina, primary effectiveness success was demonstrated in 4 subjects (4/10, 40.0%) for the Reducer group and 1 subject in the control group (1/7, 14.3%), with the Reducer group reporting 2 subjects (2/10, 20%) with an improvement of 3 CCS grades.

Only 3 subjects in the Reducer group (3/10, 30.0%) compared to 4 subjects in the Control group (4/7, 57.1%) reported an improvement of one CCS grade, and 5 subjects in both the Reducer and the Control groups demonstrated an improvement of 1 or 2 CCS grades (5/10, 50% vs. 5/7, 71.4%, respectively). As there were only 17 subjects with CCS grade IV angina, it is difficult to draw clinical conclusions regarding these results.

Table 21. Change in CCS Grade based on CCS Grade at Enrollment

All Subjects at Initiation of Study – n (%)	**Reducer N=52**	**Control N=51***
No change from CCS grade at 6 months	13 (25.0)	24 (47.1)
Improved one or more CCS angina grades at 6 months	37 (71.2)	22 (43.1)
Improved at least two CCS angina grades at 6 months**	18 (34.6)	8 (15.7)
Increase in one CCS angina grade at 6 months	2 (3.8)	5 (9.8)
CCS Grade IV Subjects at Initiation of Study – n (%)	**N=10**	**N=7**
From CCS IV to CCS III at 6 months	3 (30.0)	4 (57.1)
From CCS IV to CCS II at 6 months	2 (20.0)	1 (14.3)
From CCS IV to CCS I at 6 months	2 (20.0)	0 (0.0)
No change from CCS grade of IV at 6 months	3 (30.0)	2 (28.6)
Improved one or more CCS angina grades at 6 months	7 (70.0)	5 (71.4)
Improved at least two CCS angina grades at 6 months**	4 (40.0)	1 (14.3)
CCS Grade III Subjects at Initiation of Study – n (%)	**N=42**	**N=44***
From CCS III to CCS IV at 6 months	2 (4.8)	5 (11.4)
From CCS III to CCS II at 6 months	16 (38.1)	10 (22.7)
From CCS III to CCS I at 6 months	14 (33.3)	5 (11.4)
From CCS III to CCS 0 at 6 months	0 (0.0)	2 (4.5)
No change from CCS grade of III at 6 months	10 (23.8)	22 (50.0)
Improved one or more CCS angina grades at 6 months	30 (71.4)	17 (38.6)
Improved at least two CCS angina grades at 6 months**	14 (33.3)	7 (15.9)

* One control subject died prior to their final visit and was removed from this table.
** COSIRA trial primary endpoint

7.3.4.2 Dobutamine Stress Echocardiography and Wall Motion Score Index

Dobutamine stress echocardiography WMSI was calculated using a total of 16 segments (basal and mid–anteroseptum, anterior, anterolateral, inferolateral, inferior, inferoseptum; apical – septal, anterior, lateral, inferior) with each segment scored 1 through 5 (1 – normal, 2 – hypokinetic, 3 – akinetic, 4 – dyskinetic and 5 – aneurysmal). The scores for each segment were summed, and the total was divided by the number of segments analyzed. Additionally, since the

Reducer is placed in the CS distal to right coronary artery venous drainage, a modified left coronary artery (LCA) WMSI was calculated as described above using only the 11 segments attributed to the LCA system (basal and mid–anteroseptum, anterior, anterolateral, infer septum; apical–septal, anterior, lateral). The WMSI and modified LCA WMSI were calculated on both resting and stress images. The DSE testing was conducted under the acquisition protocol established by the core lab.

Modified LCA WMSI (stress) results using both the ITT and PP populations showed a decrease in WMSI (baseline to 6-month follow-up), with mean decreases of 0.18 and 0.09 in the Reducer and Control groups, respectively. Mean improvement in the Reducer group was 12.3% vs. 6.6% in the Control group. Summary tables for the DSE WMSI analysis on the ITT population are provided in Table 22 and Table 23.

Table 22. DSE WMSI (Change from Baseline to 6MFU, Paired Data) – ITT

DSE	Reducer	Control
Resting WMSI (RWMSI)	**N=44**	**N=36**
Baseline – mean (SD)	1.37 (0.42)	1.30 (0.32)
6-month follow-up – mean (SD)	1.30 (0.34)	1.29 (0.36)
Δ (baseline to 6MFU) – mean (SD)	-0.07 (0.33)	-0.01 (0.269)
% Δ (baseline to 6MFU)	**-4.82%**	**-0.66%**
Resting Modified LCA (RMLCA)-WMSI	**N=45**	**N=38**
Baseline – mean (SD)	1.26 (0.49)	1.23 (0.33)
6-month follow-up – mean (SD)	1.29 (0.40)	1.19 (0.38)
Δ (baseline to 6MFU) – mean (SD)	0.03 (0.35)	-0.04 (0.42)
% Δ (baseline to 6MFU)	**2.54%**	**-3.33%**
Stress WMSI (SWMSI)	**N=44**	**N=35**
Baseline – mean (SD)	1.55 (0.47)	1.47 (0.34)
6-month follow-up – mean (SD)	1.31 (0.37)	1.32 (0.36)
Δ (baseline to 6MFU) – mean (SD)	-0.23 (0.39)	-0.15 (0.35)
% Δ (baseline to 6MFU)	**-14.84%**	**-10.20%**
Stress Modified LCA (SMLCA)-WMSI	**N=45**	**N=38**
Baseline – mean (SD)	1.46 (0.56)	1.31 (0.35)
6-month follow-up – mean (SD)	1.28 (0.43)	1.22 (0.42)
Δ (baseline to 6MFU) – mean (SD)	-0.18 (0.46)	-0.09 (0.44)
% Δ (baseline to 6MFU)	**-12.33%**	**-6.56%**

Table 23. DSE WMSI (Change from Baseline to 6MFU, LOCF) – ITT

DSE	Reducer	Control
Resting WMSI-WMSI	**N=49**	**N=45**
Baseline – mean (SD)	1.38 (0.43)	1.28 (0.30)
6-month follow-up – mean (SD)	1.32 (0.36)	1.27 (0.34)
Δ (baseline to 6MFU) – mean (SD)	-0.06 (0.31)	-0.01 (0.24)
% Δ (baseline to 6MFU)	**-4.28%**	**-0.54%**
Resting MLCA-WMSI	**N=49**	**N=46**
Baseline – mean (SD)	1.31 (0.48)	1.22 (0.32)

DSE	Reducer	Control
6-month follow-up – mean (SD)	1.32 (0.43)	1.27 (0.32)
Δ (baseline to 6MFU) – mean (SD)	0.01 (0.30)	-0.01 (0.35)
% Δ (baseline to 6MFU)	**0.72%**	**-0.98%**
Stress WMSI	**N=48**	**N=44**
Baseline – mean (SD)	1.54 (0.47)	1.44 (0.39)
6-month follow-up – mean (SD)	1.33 (0.39)	1.32 (0.40)
Δ (baseline to 6MFU) – mean (SD)	-0.21 (0.38)	-0.12 (0.32)
% Δ (baseline to 6MFU)	**-13.64%**	**-8.33%**
SMLCA-WMSI	**N=48**	**N=46**
Baseline – mean (SD)	1.50 (0.53)	1.30 (0.43)
6-month follow-up – mean (SD)	1.31 (0.46)	1.26 (0.44)
Δ (baseline to 6MFU) – mean (SD)	-0.19 (0.41)	-0.04 (0.35)
% Δ (baseline to 6MFU)	**-12.67%**	**-3.23%**

7.3.4.3 Seattle Angina Questionnaire

Quality of Life scores for the ITT population show mean improvement (baseline to 6-month follow up) of 18.6 (43.9%) and 7.2 (15.7%) in the Reducer and Control groups, respectively. For the ITT population using LOCF, the mean improvement (baseline to 6-month follow up) was reported as 17.6 (41.6%) and 7.6 (16.2%) in the Reducer and Control groups, respectively. Anginal stability in the ITT population showed a mean improvement of 42.9% vs. 18.8%, and anginal frequency scores improved 16.1% vs. 8.4%. Summary tables for the SAQ analysis on the ITT population and ITT using LOCF population are provided in Table 24 and Table 25, respectively.

Table 24. SAQ (Changes from Baseline to 6MFU, Paired Data) – ITT

SAQ	Reducer	Control
Physical Limitations	**N=48**	**N=44**
Baseline – mean (SD)	47.9 (24.4)	44.7 (24.1)
6-month follow-up – mean (SD)	57.6 (27.7)	52.5 (26.3)
Δ (baseline to 6MFU) – mean (SD)	9.7 (20.5)	7.8 (22.4)
% Δ (baseline to 6MFU)	**20.3%**	**17.4%**
Anginal Stability	**N=49**	**N=45**
Baseline – mean (SD)	42.9 (22.6)	38.3 (26.1)
6-month follow-up – mean (SD)	61.2 (28.1)	47.8 (26.3)
Δ (baseline to 6MFU) – mean (SD)	18.4 (33.0)	9.4 (37.7)
% Δ (baseline to 6MFU)	**42.9%**	**24.6%**
Anginal Frequency	**N=49**	**N=45**
Baseline – mean (SD)	42.9 (24.8)	47.3 (28.4)
6-month follow-up – mean (SD)	59.0 (28.4)	58.9 (28.1)
Δ (baseline to 6MFU) – mean (SD)	16.1 (29.0)	11.6 (25.3)
% Δ (baseline to 6MFU)	**37.6%**	**24.4%**
Treatment Satisfaction	**N=49**	**N=45**
Baseline – mean (SD)	79.7 (18.3)	78.0 (18.2)

SAQ	Reducer	Control
6-month follow-up – mean (SD)	82.4 (17.1)	80.8 (19.6)
Δ (baseline to 6MFU) – mean (SD)	2.7 (17.1)	2.8 (16.1)
% Δ (baseline to 6MFU)	**3.4%**	**3.6%**
Quality of Life	**N=48**	**N=45**
Baseline – mean (SD)	42.4 (19.8)	45.9 (20.7)
6-month follow-up – mean (SD)	60.9 (23.6)	54.6 (27.4)
Δ (baseline to 6MFU) – mean (SD)	18.6 (26.5)	8.7 (23.2)
% Δ (baseline to 6MFU)	**43.9%**	**18.9%**

* Table generated by FDA.

Table 25. SAQ (Changes from Baseline to 6MFU, LOCF) – ITT

SAQ	Reducer	Control
Physical Limitations	**N=51**	**N=47**
Baseline – mean (SD)	47.4 (24.7)	45.4 (24.5)
6-month follow-up – mean (SD)	56.5 (27.1)	52.8 (26.7)
Δ (baseline to 6MFU) – mean (SD)	9.2 (20.2)	7.4 (22.1)
% Δ (baseline to 6MFU)	**19.4%**	**16.3%**
Anginal Stability	**N=51**	**N=48**
Baseline – mean (SD)	43.1 (22.4)	39.1 (25.7)
6-month follow-up – mean (SD)	61.3 (27.5)	47.4 (25.9)
Δ (baseline to 6MFU) – mean (SD)	18.1 (32.4)	8.3 (37.3)
% Δ (baseline to 6MFU)	**42.0%**	**21.2%**
Anginal Frequency	**N=51**	**N=48**
Baseline – mean (SD)	43.7 (25.9)	46.7 (28.8)
6-month follow-up – mean (SD)	59.0 (29.3)	57.7 (29.1)
Δ (baseline to 6MFU) – mean (SD)	15.3 (28.9)	11.0 (24.9)
% Δ (baseline to 6MFU)	**35.0%**	**23.6%**
Treatment Satisfaction	**N=51**	**N=48**
Baseline – mean (SD)	79.7 (18.6)	77.6 (18.1)
6-month follow-up – mean (SD)	82.6 (17.6)	80.4 (19.3)
Δ (baseline to 6MFU) – mean (SD)	2.9 (16.6)	2.9 (15.8)
% Δ (baseline to 6MFU)	**3.6%**	**3.7%**
Quality of Life	**N=51**	**N=48**
Baseline – mean (SD)	42.3 (19.7)	46.9 (20.6)
6-month follow-up – mean (SD)	60.0 (23.7)	54.5 (27.0)
Δ (baseline to 6MFU) – mean (SD)	17.6 (26.2)	7.6 (23.3)
% Δ (baseline to 6MFU)	**41.6%**	**16.2%**

7.3.4.4 Exercise Tolerance Testing

A bicycle ergometry stress test, adapted from the Asymptomatic Cardiac Ischemia Pilot (ACIP) protocol, was performed by the ETT core lab using standard operating procedures. The following parameters were recorded at baseline and 6-month follow-up for comparative analysis:

- Total exercise duration: the time (in seconds) that the patient exercised before being no longer able to continue.
- Time to 1 mm ST segment depression: the time that the patient exercised until exhibiting ST segment depression.
- Maximal ST segment depression: the total measurement of ST segment depression exhibited by the patient while undergoing exercise testing.
- Metabolic equivalent to tasks (METs): essentially a measurement of the body's metabolic rate.
- Double product: heart rate multiplied by systolic blood pressure, used as an estimate of myocardial work; proportional to myocardial oxygen consumption.

Paired data analysis of the ITT population showed a mean increase in the Reducer group of 64.7 seconds vs. a mean increase in the Control group of 4.3 seconds. This is an increase of 14.5% vs. 1.0% in the Reducer and Control groups, respectively. With respect to time to ST segment depression, the Reducer group improved 76.3 seconds vs. a 33.8 second improvement in the Control group (18.0% vs. 8.2%, respectively). The PP analysis also demonstrated similar results. However, as will be discussed in Section 7.3.4.5, this data has significant amounts of missing information that limit its applicability. Summary tables for the ETT analysis on the ITT population are provided in Appendix 10.3.

7.3.4.5 Missing Information

While all subjects were expected to have DSE, SAQ, and ETT data collected as part of their baseline and 6-month follow up, some of these analyses had a substantial amount of missing data, specifically related to the ETT analysis. Table 26 was generated by FDA based on the raw data provided in the submission and provides an overview of the missing information for the ITT population.

Table 26. Missing Information Noted for the ITT Population

	Reducer Group, N=52	**Control Group, N=52**
Missing Testing DSE Data[*] – n (%)		
Missing resting WMSI	8 (15.4)	16 (30.8)
Missing resting Modified LCA	7 (13.5)	14 (26.9)
Missing stress WMSI	8 (15.4)	17 (32.7)
Missing modified LCA	7 (13.5)	14 (26.9)
Missing Testing SAQ Data[*#] – n (%)		
Missing physical limitations	4 (7.7)	8 (15.4)
Missing anginal stability	3 (5.8)	7 (13.5)
Missing anginal frequency	3 (5.8)	7 (13.5)
Missing treatment satisfaction	3 (5.8)	7 (13.5)
Missing quality of life	4 (7.7)	7 (13.5)
Missing Testing ETT Data[*] – n (%)		
Missing total exercise duration	15 (28.8)	12 (23.1)
Missing time to 1 mm ST depression	45 (86.5)	46 (88.5)

	Reducer Group, N=52	Control Group, N=52
Missing time to max ST depression	37 (71.2)	39 (75.0)

* Missing data is limited to subjects with a missing assessment at baseline or the 6-month assessment.

\# One control subject (b) (6) was reported to have had their 30-day SAQ assessment prior to their baseline assessment. This subject was removed from this analysis as the data timing could not be confirmed.

As shown above, the results presented from these imputation methods either were similar to the results without imputation of missing data (i.e., "paired data") or had significant missing data, which could impact the validity of the imputation. In addition, as there was neither pre-specified statistical hypotheses for these secondary endpoints nor a multiplicity adjustment strategy to account for these tests, the tipping point analysis is difficult to interpret. Based on these limitations, FDA believes that focus should be placed on the "paired data" provided with this analysis.

Panel Question: While not included as a primary endpoint, changes in ischemia were evaluated as important secondary endpoints using ETTs. The COSIRA study was not powered to detect an improvement in ischemia. While these data are informative, there is a significant amount of missing information as shown in Table 26. Given the limited sample size and the level of information missing from the ETT testing, the Panel will be asked to discuss any conclusions that can be drawn from this information. The Panel will also be asked if additional premarket ischemia assessment data collection should be performed.

7.3.5 Subgroup Analyses

The following subgroups were pre-specified for the primary endpoint:

- Baseline left LVEF (20–40%, 41–50%, 51–60%, 61–70%, 71–90%)
- Previous CABG (Yes, No)
- Diabetes (Yes, No)
- Gender (Female, Male)
- Age in years (30–60, 61–70, 71–90)
- Race (Asian, White, Unknown)
- Center (Site 1 through 11)

There were four subgroups reported to have differences between the groups: subjects with previous CABG, subjects without diabetes, whites, and subjects at Site 1, with the outcomes favoring the Reducer over Control. These analyses lack a pre-specified statistical hypothesis or multiplicity adjustment for type I error control and are not included in this Summary.

7.3.6 Alternative Efficacy Analysis

7.3.6.1 Observational Measures using Thallium/MIBI SPECT

Results using Thallium/MIBI SPECT performed in a sub-set of study subjects numerically favored the Reducer group; however, these results did not have an associated prespecified hypothesis test, nor did they trend toward significance for either paired data or LOCF. Summary tables for the thallium/MIBI SPECT analysis are provided in Table 27 and Table 28.

Table 27. SPECT (Changes from Baseline to 6MFU, Paired Data) – ITT

	Reducer	**Control**
Summed Rest Score (SRS)	**N=35**	**N=27**
Baseline – mean (SD)	5.71 (6.66)	5.26 (9.13)
6-month follow-up – mean (SD)	5.11 (6.83)	5.04 (7.72)
Δ (baseline to 6MFU) – mean (SD)	-0.60 (4.93)	-0.22 (4.71)
% Δ (baseline to 6MFU)	**-10.51%**	**-4.18%**
Summed Stress Score (SSS)	**N=37**	**N=29**
Baseline – mean (SD)	11.03 (7.83)	9.79 (9.50)
6-month follow-up – mean (SD)	10.14 (7.99)	8.69 (8.17)
Δ (baseline to 6MFU) – mean (SD)	-0.89 (4.14)	-1.10 (6.53)
% Δ (baseline to 6MFU)	**-8.07%**	**-11.24%**
Summed Difference Score (SDS)	**N=35**	**N=27**
Baseline – mean (SD)	5.51 (4.95)	4.74 (5.23)
6-month follow-up – mean (SD)	5.00 (4.28)	3.89 (4.23)
Δ (baseline to 6MFU) – mean (SD)	-0.51 (3.39)	-0.85 (4.56)
% Δ (baseline to 6MFU)	**-9.26%**	**-17.93%**

Table 28. SPECT (Changes from Baseline to 6MFU, LOCF) – ITT

	Reducer	**Control**
Summed Rest Score (SRS)	**N=37**	**N=30**
Baseline – mean (SD)	5.49 (6.56)	5.30 (8.86)
6-month follow-up – mean (SD)	4.92 (6.70)	5.10 (7.57)
Δ (baseline to 6MFU) – mean (SD)	-0.57 (4.79)	-0.20 (4.46)
% Δ (baseline to 6MFU)	**-10.38%**	**-3.77%**
Summed Stress Score (SSS)	**N=38**	**N=31**
Baseline – mean (SD)	10.82 (7.84)	9.68 (9.22)
6-month follow-up – mean (SD)	9.95 (7.97)	8.65 (7.94)
Δ (baseline to 6MFU) – mean (SD)	-0.87 (4.09)	-1.03 (6.31)
% Δ (baseline to 6MFU)	**-8.04%**	**-10.64%**
Summed Difference Score (SDS)	**N=37**	**N=30**
Baseline – mean (SD)	5.30 (4.91)	4.70 (5.07)
6-month follow-up – mean (SD)	4.81 (4.25)	3.93 (4.14)
Δ (baseline to 6MFU) – mean (SD)	-0.49 (3.30)	-0.77 (4.33)
% Δ (baseline to 6MFU)	**-9.19%**	**-16.38%**

7.3.6.2 CT Angiography

CT angiography was performed at 6 months for 37 of 50 (74.0%) subjects that received the Reducer device. While the study protocol indicated that CT angiography should be collected at the 6-month follow-up visit, the sponsor was unable to provide this information for 13 subjects treated in the Reducer group. In 37 of 37 subjects (100%), the Reducer was located in the CS and showed no signs of migration. In 35 of 37 subjects (94.6%), contrast flow could be seen in the Reducer, demonstrating that the device was patent. In the subjects where flow was not seen through the Reducer, the sponsor indicated that the imaging and opacification of the CT study were not optimal. In 16 of 37 (43.2%) subjects, it was reported that thrombus was present in the Reducer. Of the devices with thrombus reported, none were occluded, and only 2 showed a luminal narrowing of more than 50%. Commenting on the interpretation of data, the CT Angio Core Lab representative Dr. Gaby Weissman of MedStar Health Research Institute stated, "when examining the CT angiograms to determine if there was thrombus present, a decision was made early on in the reading process to refer to areas of low CT density on the device as thrombus from a coding standpoint." The Core Lab has determined that "the low density areas seen may represent other diagnoses and it is not possible to differentiate between thrombus and fibrosis." According to the Core Lab, "the low Hounsfield unit areas may represent either thrombus or fibrosis. In addition, the device may have artifact associated with it (motion or attenuation), complicating interpretation… Artifact, in the case of small findings, may play a role or if there is significant motion artifact as well."

Panel Question: It should be noted that 15 of the 52 subjects (28.8%) implanted with the Reducer device did not have CT angiographic follow-up. Of the 37 subjects that did receive imaging, 16 (43.2%) were reported to have thrombus present in the device. If a worst-case approximation is used, this could result in an estimated 60.0% (31/52) of subjects with thrombus formation. The clinical significance of device-related thrombus is unknown. Additionally, information on the presence or degree of severity of a CS stenosis or pressure gradient across the device was not assessed, such that no correlations could be made between clinical outcomes and the degree of CS stenosis and CS pressure gradient. Given the level of missing information and uncertainties noted in the COSIRA analyses, the Panel will be asked to discuss and make recommendations on the need for additional imaging data to support a reasonable assurance of safety and effectiveness for the Reducer System.

7.3.6.3 Cardiac MRI

Subjects enrolled at the Montreal Heart Institute (MHI) were offered participation in a cardiac magnetic resonance imaging (CMR) sub-study that was intended to quantify the variation in myocardial tissue oxygenation in response to CS Reducer implantation. Participants underwent a perfusion CMR at baseline and at 6 months following randomization. The following parameters were evaluated on all subjects both pre- and post-therapy:

- Left ventricular function
- Left ventricular volumes
- Right ventricular function

- Right ventricular volumes
- Delayed enhancement (late gadolinium enhancement [LGE])
- Wall motion abnormalities
- Myocardial perfusion

Initially, it was planned that all eligible subjects would undergo CMR at baseline, but only participants treated with the Reducer would undergo a follow-up CMR at 6 months. Of the 23 participants randomized at the MHI, 11 underwent Reducer implantation (12 randomized to implantation minus one failed implantation). Because several individuals declined participation, only 5 participants underwent both the baseline and follow-up CMR (Table 29). Before and after measurements were compared using the Wilcoxon signed-rank test. In the absence of a pre-specified statistical analysis plan and due to the large amount of missing data, statistical inferences should be drawn with caution.

Table 29. Cardiac MRI Sub-Study Results

Patient	LVEF (%)		LVEDV (ml)		LVESV (ml)		SV (ml)		RVEF (%)		RVEDV (ml)		RVESV (ml)		SV (ml)		WM Score		LGE %	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
1	39	62	219	248	133	95	86	152	50	60	200	180	100	71	100	109	13	4	0.31	0.26
2	45	53	174	155	96	73	78	82	40	54	136	165	82	75	54	90	22	15	0.32	0.31
3	37	39	211	219	132	133	78	86	38	43	137	132	85	75	52	57	25	18	0	0.4
4	55	73	132	137	59	37	73	100	62	54	137	149	52	68	85	81	11	5	0.31	0.07
5	50	59	83	141	42	58	41	82	58	50	140	177	59	89	81	88	11	7	0.01	0

LVEF – Left Ventricular Ejection Fraction
LVEDV – Left Ventricular End-Diastolic Volume
LVESV – Left Ventricular End-Systolic Volume
SV – Stroke Volume
RVEF – Right Ventricular Ejection Fraction
RVEDV – Right Ventricular End-Diastolic Volume
RVESV – Right Ventricular End-Systolic Volume
WM – Wall Motion
LGE – Late Gadolinium Enhancement

7.3.7 Protocol Deviations

A total of 248 protocol deviations occurred during the study. The majority of the protocol deviations (83/248, or 33.5%) were classified as "other." The sponsor stated the vast majority of deviations should have been categorized as "follow-up/assessment not performed according to protocol" instead of selecting "other." These deviations included individual tests that were not performed for a number of reasons, or individual tests that may have been performed outside the time window.

Table 30. Protocol Deviations

Deviation – n (%)	Total Number of Deviations* N=248	Total # of Subjects with Deviation	
		Reducer Group N=52	Control Group N=52
Follow-up completed outside of window	73 (29.4)	22 (42.3)	25 (48.1)
Follow-up not completed†	12 (4.8)	5 (9.6)	3 (5.8)

Deviation – n (%)	Total Number of Deviations* N=248	Total # of Subjects with Deviation	
		Reducer Group N=52	Control Group N=52
Follow-up/assessment not performed according to protocol	65 (26.2)	19 (36.5)	19 (36.5)
Subject did not meet inclusion/exclusion criteria	15 (6.0)‡	5 (9.6)	6 (11.5)‡
Other^	83 (33.5)	21 (40.4)	23 (44.2)

* Total number of deviations differs from number of subjects with deviations as some subjects had multiple deviations recorded

† In 11 of the 12 subjects, one or more clinical assessments were not completed. One subject had no 3-month follow up

‡ This total does not include subject (b) see Table 10

^ This category includes one subject who had a PCI 174 days pre-enrollment. A waiver was given by the Sponsor to include this subject in the study

Table 31. Inclusion/Exclusion Deviations

Inclusion/Exclusion Deviation – n	Total # of Deviations to Inclusion/ Exclusion Criteria N=16	
	Reducer Group N=8	Control Group N=8
No 1 mm ST segment depression*	2	3
Successful PCI or CABG within 6 months of enrollment	3†	4^
Acute coronary syndrome within 3 months of enrollment	3§	0
No positive DSE‡	0	1

* The original protocol included a 1 mm or greater ST segment depression requirement, which was later removed. These subjects were enrolled prior to that amendment.

† In one subject (b) (6), prior approval for deviation was obtained

‡ This subject (b) (6) was enrolled after Amendment 3, which required positive DSE instead of at least 1 mm ST segment depression

^ In one subject (b) (6), PCI was performed 174 days before enrollment, however a waiver was provided to the site

§ In one subject (b) (6) this was due to a troponin rise following PCI and thus would not be considered "true" acute coronary syndrome

7.4 Clinical Data Limitations

While the COSIRA trial was a prospective, multicenter, randomized, double-blind, sham-controlled (1:1 randomization ratio), clinical study of the safety and effectiveness of the Reducer system, FDA has identified several limitations, which have been previously provided to the sponsor through interactions and the major deficiency letter for the current submission. The COSIRA trial (104 total subjects enrolled, with 52 devices implanted) may not have been large enough to provide reasonable assurance that the results reflect likely outcomes for most patients. Additionally, concerns regarding the subjective primary endpoint and limited statistical confidence in the objective secondary effectiveness measures for this intervention raise the question of whether additional data are needed. These concerns were also shared by Verheye et al. (2015), who published the findings of the COSIRA trial and stated that the "study was not

statistically powered to detect an improvement in ischemia by means of objective measures such as stress testing or wall-motion index. A larger trial would be necessary to show such a benefit."

In clinical trials targeting angina, there is a well-documented history of cardiac interventional pivotal trials failing to demonstrate clinical effectiveness results that were observed in prior smaller investigations. Examples include internal mammary artery implants and ligation (Langston et al. 1972; Balcon et al. 1970; Björk et al. 1968), transmyocardial laser revascularization (TMR) (Leon et al. 2005), and gene therapy (Povsic et al. 2016; Wojakowski Wojciech et al. 2017; Henry et al. 2017; Jimenez-Quevedo Pilar et al. 2014).

Similarly, there is a large placebo effect that has been shown in previous blinded studies in the field of refractory angina. Angina can be a placebo-responsive condition, as evidenced by TMR and IMA trials. A high placebo response rate was seen in the COSIRA trial, in which 42.3% of control subjects had a reduction in CCS class of at least one grade at 6 months. The COSIRA study lacked a blinding questionnaire for subjects at the end of the study to help better evaluate the blinding success.

A high percentage of COSIRA subjects (65.4%) did not experience a reduction of two CCS classes, as prespecified as the primary measure of effectiveness, while 25% experienced no reduction in CCS class. It is not clear why some subjects respond or do not respond to device treatment. Incomplete Reducer endothelization has been postulated as a cause of lack of effectiveness in some patients (Zivelonghi et al. 2019). Other hypotheses include differences in subjects with respect to accessory venous drainage, angina due to lesions in the right coronary artery, symptoms due to heart failure (rather than ischemia), or non-anginal chest pain. The high rate of subjects failing to meet the primary study success criteria suggests that additional data are needed to identify the patient population most likely to have a clinically meaningful benefit with the Reducer device (considering risks of the implant procedure and the device). Similarly, FDA is concerned regarding the characterization of subjects enrolled in COSIRA as "no-option" patients, as this determination can be difficult and can vary depending on the specific criteria used and medical expertise available. Since the definition of "no-option" patients can vary and options for revascularization continuously evolve, FDA is seeking Panel input regarding the characteristics of the optimal patient population for the Reducer.

The primary endpoints for the COSIRA trial were evaluated at 6 months, with longer-term data planned for collection in an OUS postmarket study (REDUCER-I). While the data provided from this postmarket study are helpful as an adjunctive data set, its observational nature, potentially high placebo response rate, and the absence of a concurrent control group makes it challenging to draw conclusions regarding long-term Reducer effectiveness.

Statistical analysis limitations were also notable. The interim analysis initially provided by the sponsor indicated that after the initial 62 subjects were enrolled, the p-value was determined to be 1.000 (χ^2=0.000, df=1). After an additional 42 subjects were enrolled and the study halted enrollment, the sponsor reported a final p-value of 0.024. However, upon FDA's request for additional information regarding this significant change in p-value, the sponsor indicated that "the interim report was produced by persons no longer involved with the sponsor, so we are unable to gather additional information related to creation of the interim analysis report." As part of an interactive communication with the sponsor during the initial review for this submission,

FDA requested additional information regarding the primary and interim statistical analyses. During this interaction, FDA was informed that while the raw data was available and provided as part of the submission, the statistical analyses had been performed by a CRO that no longer possessed any study records. Therefore, additional information regarding the statistical analysis methods was unavailable for FDA to confirm or validate the results.

As discussed in Section 7.2.4.3, missing data imputation was performed using the LOCF method for secondary endpoints. However, there were no pre-specified statistical hypotheses for these secondary endpoints, nor a multiplicity adjustment strategy to account for the additional hypothesis tests performed. Therefore, statistical inferences for these endpoints should be drawn with caution, and the interpretation of the imputed analysis is unclear. Additionally, the LOCF method assumes the prior information continued unchanged. Given the novelty of the subject device and the limited clinical information regarding long-term outcomes, the LOCF analysis may not be appropriate, as it is unknown how patients will perform long-term.

Lastly, it is important that clinical trial participants reflect the diversity of the population that may receive this intervention. The COSIRA study enrolled primarily white (86.5%) males (80.8%). Given the small sample size of the COSIRA study, it is challenging for FDA to draw conclusions regarding potential differences in outcomes based on race/ethnicity and/or gender that may be important for determining a reasonable assurance of Reducer safety and effectiveness for the US population.

Panel Question: Study limitations have been discussed with the sponsor and provided most recently as part of FDA's Major Deficiency letter, dated March 30, 2020. In this letter, FDA identified the limitations regarding whether clinical study data support a reasonable assurance of safety and effectiveness. FDA commented that based on the number and importance of the limitations, additional clinical data may be needed to support a PMA application. As noted in Section 5.3, the sponsor requested that if FDA has remaining uncertainty regarding the provided information being able to support a reasonable assurance of safety and effectiveness, they would like the opportunity to discuss these concerns as part of an advisory committee meeting.

As discussed above in Section 5, FDA worked with the sponsor to develop the COSIRA-II protocol (synopsis in Appendix D) that is currently approved under an IDE application. However, the sponsor chose to forgo this additional data collection, believing the current data set to be sufficient. The Panel will be asked to discuss and make recommendations about whether additional premarket data from a randomized sham-controlled clinical study is needed to support the safety and effectiveness of the Neovasc Reducer System given the concerns and limitations with the currently collected data. If additional premarket clinical data are recommended, the Panel will be asked to comment on and make recommendations regarding whether the recommended data could be obtained from using a protocol similar to that of COSIRA-II.

7.5 Adjunctive Data Provided in the PMA

Additional OUS postmarket observational, open label, non-randomized data collection is ongoing to assess long-term outcomes on the use of the Reducer in the REDUCER-I study. The planned enrollment is 400 subjects with enrollment anticipated estimated to be completed in 2022. The first subject was enrolled on March 14, 2016, and as of March 12, 2020, there were 241 subjects enrolled. While an interim analysis report containing summary level information was provided to FDA, a detailed dataset with patient-level information has not been provided to FDA for review. Thus, FDA was unable to validate and confirm the results provided in the report.

The study population includes:

- Subjects with refractory angina pectoris who demonstrate objective evidence of reversible myocardial ischemia, who have limited or no options for revascularization (Arm 1, n=191 subjects enrolled)
- Subjects who have received the Reducer in the COSIRA study (Arm 2, n=11 subjects enrolled)
- Subjects implanted under CE Mark prior to the REDUCER-I study (Arm 3, n=39 subjects enrolled)

Arm 1: Subjects are enrolled prior to receiving the Reducer implant. Subjects successfully implanted are followed from baseline and procedure to 30 days (phone visit), 6- and 12-months post implant and annually through 5 years.

This arm includes prospective data collection only. Enrollment is ongoing in this arm of the study.

Arm 2: Subjects who were previously enrolled and treated with the Reducer during the COSIRA study, and consent to participate in the REDUCER-I study. This arm includes both retrospective and prospective data collection.

- Data previously collected from the treatment arm of the COSIRA study (baseline, procedure, 30 days and 6-month post implant) is included in this arm.
- Retrospective data (prior to consent) and/or prospective data (after consent) will be collected at 12 months post implant and annually through 5 years post-implant.

Enrollment is complete in Arm 2 of the study.

Arm 3: Subjects who received a Reducer under CE Mark (unrelated to the COSIRA study), meet eligibility, and consent to participate in the REDUCER-I study. This arm includes both retrospective and prospective data collection.

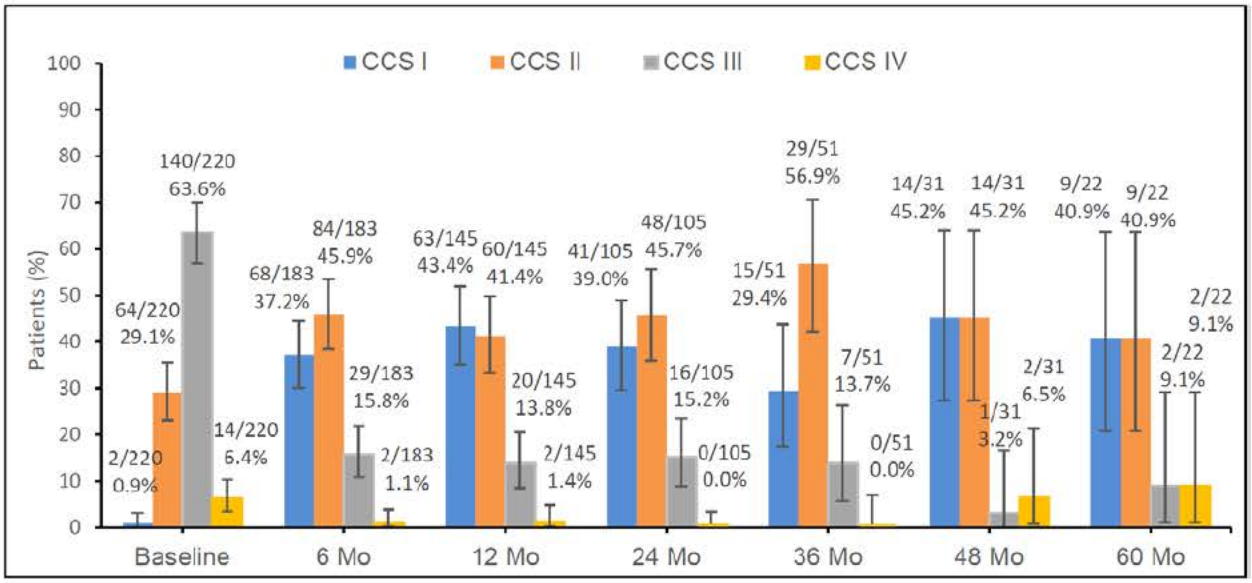
- Available baseline and procedure data will be collected retrospectively.
- Retrospective and/or prospective data will be collected at 30 days, 6 months, and 12 months post implant and annually through 5 years post implant. Enrollment is complete in Arm 3 of the study.

As of the March 12, 2020 interim analysis, the REDUCER-I study has enrolled subjects that are predominately male (81.1%) with an average age at enrollment of 68.2 years. The majority of subjects had a baseline CCS grade of III (63.6%); 7.2% of subjects had a baseline CCS grade of IV, and 28.2% had a CCS grade of II. At the interim assessment, the results show positive trends with 24.7% of subjects (41 of the 166 available for assessment) reporting an improvement of two or more CCS classes at 6 months. Follow-up will continue to 5 years; at this time 5-year data is available for 8.3% of subjects (20/241), and 15.4% (44/241) of subjects have data available at 3 years (Table 32). Figure 9 provides information regarding the percentage of subjects by CCS grade through 5 years.

able 32. CCS Class from Baseline Over Time – All Arms (Paired Data)

CCS Class Change from Baseline[1]	6 Month	12 Month	24 Month	36 Month	48 Month	60 Month
Worsening from Baseline	2.2% (4/181)	1.4% (2/140)	1.0% (1/98)	0.0% (0/44)	0.0% (0/26)	0.0% (0/20)
No Change from Baseline	28.2% (51/181)	24.3% (34/140)	17.3% (17/98)	29.5% (13/44)	15.4% (4/26)	20.0% (4/20)
≥1 Class Improvement	69.6% (126/181)	74.3% (104/140)	81.6% (80/98)	70.5% (31/44)	84.6% (22/26)	80.0% (16/20)
≥2 Classes Improvement	24.3% (44/181)	25.7% (36/140)	30.6% (30/98)	34.1% (15/44)	46.2% (12/26)	35.0% (7/20)
≥3 Classes Improvement	0.6% (1/181)	0.7% (1/140)	0.0% (0/98)	0.0% (0/44)	0.0% (0/26)	0.0% (0/20)

[1] Categorical data are presented as % (n/N).



(95% CI are provided; however, these these intervals should be interprated with caution as a complete statistical plan with prespecified hypothesis tests and multiplicity corrections have not been provided.)

Figure 9. Percentage of Subjects by CCS Grade through 60 Months - All Arms.

The CEC has adjudicated 160 events. A total of 102 (63.8%) were determined to be endpoint-related, per the CEC definitions. All events were evaluated for device and/or procedure relatedness. Of the 160 adjudicated events, 101 SAEs (81 endpoint-related and 20 non endpoint-related) were reported in 59 subjects (24.5%), with 3.3% (N=8 subjects) adjudicated as procedure-related and 1.2% (N=3 subjects) as device-related. There have been 13 deaths reported in the study with 10 adjudicated by the CEC as non-device and/or procedure related and 3 deaths awaiting adjudication. Six of the deaths have been adjudicated as cardiac-related. There were 32 events that were adjudicated as being MACE events and one (1/288, 0.4%) was adjudicated as being procedure and device-related.

Table 33. Endpoint-Related Events

Event (n/N, (%))	**Events**	**Subjects**	**Procedure - related** Subjects	**Device-related** Subjects	**SAE Events**	**SAE Subjects**	**SAE Procedure -related** Subjects	**SAE Device-related** Subjects
Angina as an Adverse Event	66/160 (41.3%)	45/241 (18.7%)	1/241 (0.4%)	1/241 (0.4%)	45/101 (44.6%)	29/241 (12.0%)	1/241 (0.4%)	1/241 (0.4%)
Cardiac Tamponade	1/160 (0.6%)	1/241 (0.4%)	1/241 (0.4%)	1/241 (0.4%)	1/101 (1.0%)	1/241 (0.4%)	1/241 (0.4%)	1/241 (0.4%)
Death[1,2]	10/160 (6.3%)	10/241 (4.1%)	0	0	10/101 (9.9%)	10/241 (4.1%)	0	0
Myocardial Infarction	21/160 (13.1%)	16/241 (6.6%)	1/241 (0.4%)	1/241 (0.4%)	21/101 (20.8%)	16/241 (6.6%)	1/241 (0.4%)	1/241 (0.4%)
Stroke	5/160 (3.1%)	4/241 (1.7%)	0	0	5/101 (5.0%)	4/241 (1.7%)	0	0
Total	**102/160 (63.8%)**	**64/241 (26.6%)**	**3/241 (1.2%)**	**3/241 (1.2%)**	**81/101 (80.2%)**	**48/241 (19.9%)**	**3/241 (1.2%)**	**3/241 (1.2%)**

[1] 6 events were adjudicated as Cardiac Deaths

[2] If cardiac death was accompanied by another adjudicated event, only cardiac death was counted as an event

Table 34. MACE Events

Event	**Events n/N**	**Subjects n/N (%)**	**Procedure-related /Subjects n/N (%)**	**Device-related /Subjects n/N (%)**
Cardiac Death[1]	6/32	6/228 (2.6%)	0	0
Major Stroke	5/32	4/228 (1.8%)	0	0
Myocardial Infarction	21/32	16/228 (7.0%)	1/288 (0.4%)	1/228 (0.4%)
Total	32	23/228 (10.1%)	**1/288 (0.4%)[2]**	**1/228 (0.4%)[2]**

[1] Cardiac Deaths:
(b) (6) : Myocardial Infarction
(b) (6) : Other: complication of Surgical AVR and CABG (b) (6) : Arrhythmia
(b) (6) : Heart Failure

[2] (b) (6) : An MI was reported 19 days post implant and was adjudicated as Unknown device- and/or procedure-related, as the CEC did not have the documentation available to determine definitively the relationship to the device and/or procedure

There were 378 protocol deviations that occurred at 20 of the 22 currently active sites. The most frequent deviation was for a *Missed Procedure, Test or Assessment* (162 deviations), then *Procedure, Test or Assessment Out of Window* with 54 deviations and *Visit Out of Window* with 63 deviations. The most frequently *Missed Procedure/Test* were ETTs required at follow-up and resting ECGs post procedure.

While informative as adjunctive data, FDA notes the following limitations to the data collected in the REDUCER-I study:

- REDUCER-I is an open-label non-randomized study that allows for a significant placebo effect. Additionally, the study does not assess objective evidence of changes in myocardial ischemia.
- Only interim summary level data are available. Enrollment is not projected to be complete until 2022. Additionally, FDA has not reviewed any patient-level data to confirm the summary results.
- The patient population enrolled in this trial is different from the population studied in the COSIRA trial, with the REDUCER-I study enrolling a significant number of CCS Class II (56) patients, which as of March 2020, is greater than the enrollment of Class IV patients (13).
- The reported death rate is of 4.1% (10/241), MI rate 6.6% (16/241), and stroke 1.7% (4/241). Some events have not yet been adjudicated by the CEC (e.g., 3 deaths reported in the May 2020 interim report). Clinically stable patients with refractory angina despite medical therapy and without revascularization options have a modest risk of mortality overall although reported long-term clinical outcomes of such patients have been variable, likely due to heterogeneity in the criteria used to define these patients (Povsic et al. 2015). The broader enrollment criteria used to enroll many of the REDUCER-I patients may make it difficult to define a patient population at higher risk of adverse outcomes.
- Differences in medical practice, health care delivery, and patient demographics compared to the US may make REDUCER-I trial results difficult to extrapolate to a US population. Additional analysis will be needed to consider the variability in standards of care for the different markets in which data are being collected.

Additional information and tabular data are provided in Appendix B, Section 11.5.

FDA Comment: The REDUCER-I study is an observational, open-label, non-randomized, postmarket study that is currently enrolling subjects and is projected to reach complete enrollment in 2022. While this data has the potential to provide supportive information regarding the long-term performance of the Reducer system, the limitations identified above make it challenging for FDA to utilize this information to make a premarket determination regarding a reasonable assurance of safety and effectiveness for the current PMA application. Based on the information provided, FDA considers this information adjunctive but not sufficient to be included as a principal data set used to demonstrate a reasonable assurance of safety and effectiveness.

7.6 Potential Post Approval Study (PAS) Collection

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.*

Panel Question: 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 would be inappropriate to mandate an additional study where patients who lack alternative treatments would be randomized to the sham control. Given this concern, the Panel will be asked to consider if a post-approval randomized sham-controlled trial is appropriate and feasible.

8 Summary

This document provides a brief review of the treatment of angina, a description of the subject device (Neovasc Reducer™ System), a review of pre-clinical studies, and the presentation of clinical data from the pivotal study titled "The Coronary Sinus Reducer for Treatment of Refractory Angina (COSIRA)" used to support the PMA P190035. Based on the information provided, the sponsor is requesting that this device be indicated 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).

The sponsor has provided limited data from three non-GLP animal studies performed using the current device along with a prior model. While these studies provided preliminary information regarding the performance of the device, FDA's prior review of this information as part of (b) (4) raised concerns regarding the quality and consistency of the data, the level of documentation, unclear timelines, and concerns regarding the degree of tissue coverage and endothelialization of the Reducer device.

The sponsor's initial clinical experience with the Reducer device came from an OUS FIH study, performed in India and Germany. This trial was a single arm, open-label, feasibility study using a prior generation of the device. This trial enrolled 15 subjects and has collected longer term data, with some subjects contributing 12-year follow-up data. While this FIH study provided a preliminary investigation of this treatment approach, the use of a prior device design, lack of concurrent control, and the limited number of subjects makes it challenging for FDA to consider this data beyond an informative initial investigation.

The COSIRA trial was a prospective, multi-center randomized double-blind, sham-controlled (1:1 randomization ratio), clinical study performed to evaluate the safety and effectiveness of the Reducer device in the treatment of refractory angina. The primary effectiveness success rate in the ITT analysis population was 34.6% (18/52) for the Reducer group, vs. 15.4% (8/52) in the Control group. In the 52 subjects who were randomized to the Reducer group, 50/52 (96.2%) had a Reducer successfully implanted. The only death in the study was seen in the control. However, FDA remains concerned that the limited sample size may not provide reasonable assurance that the promising results reflect likely outcomes for most patients. Additionally, concerns regarding the subjective primary endpoints, limited data for a reduction in objective evidence of ischemia, no data on whether the Reducer creates a significant CS stenosis or produces a clinically meaningful CS pressure increase, dissimilarity of the patient population compared to the US population (i.e., limited number of minority and female subjects), limited statistical confidence in the effectiveness of the intervention, and the limited follow-up duration of 6 months, prompt the question if a larger, longer duration study with a population more reflective of the US CAD population may be warranted.

The current data and associated limitations also present challenges when trying to identify a patient population for which it can be determined that this device has demonstrated a reasonable assurance of safety and effectiveness. Device labeling should include information relevant to the safe and effective use of the device along with associated warnings and precautions that should be considered prior to treatment.

Because of the importance of this patient population and our desire to bring novel treatments to patients, we are seeking the Panel's input on the assessment of benefits and risks of this device. While we have shared our current thinking and summarized our assessment, FDA is seeking Panel input before rendering a final decision on the submission as to whether the information provided demonstrates a reasonable assurance of safety and effectiveness as defined in 21 CFR 860.7(d)(1) and (e)(1). Summarized, the evidence must show that when using the device properly, the evidence supports that in a significant portion of the target population, the benefits to health outweigh the risks, and there is an absence of unreasonable risk (safety), and that there are clinically significant results in a significant portion of the target population (effectiveness).

Summary to Panel: FDA is seeking discussion and recommendations on the premarket approval (PMA) P190035 application from Neovasc Medical, Inc. for the Neovasc Reducer System for the treatment of refractory angina. Importantly, the Panel will be asked to discuss and make recommendations on whether a reasonable assurance of safety and effectiveness has been established for the proposed IFU based on the totality of the pre-clinical and clinical evidence presented herein. Additionally, the Panel will be asked to comment and make recommendations on whether the proposed IFU adequately defines the proposed patient population for which the device demonstrates a reasonable assurance of safety and effectiveness. Should the Panel determine the data provided supports a reasonable assurance of safety and effectiveness for the proposed IFU, the Panel will be asked whether there should be specific contraindications, warnings, precautions, or instructions for use that should be conveyed in the Directions for Use (DFU) to ensure the safe and effective use of the Reducer System.

We look forward to the discussion at the October 27, 2020 Advisory Committee meeting.

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10 Appendix A – Tabular Information Provided for COSIRA Data

10.1 Significant Concomitant Medications

Table 35. Summary of Significant Concomitant Medications by Time Point

Subjects Taking Medication – n (%)	Reducer N=50	Control N=54*
Any Cardiac Medication		
Screening	50 (100.0)	54 (100.0)
Pre-procedural	50 (100.0)	53 (98.1)
At discharge	50 (100.0)	54 (100.0)
30 days	50 (100.0)	54 (100.0)
3 months	50 (100.0)	54 (100.0)
6 months	50 (100.0)	53 (100.0)*
ASA		
Screening	46 (92.0)	50 (92.6)
Pre-procedural	44 (88.0)	48 (88.9)
At discharge	49 (98.0)	51 (94.4)
30 days	48 (96.0)	51 (94.4)
3 months	48 (96.0)	50 (92.6)
6 months	48 (96.0)	48 (90.6)*
Clopidogrel		
Screening	30 (60.0)	28 (51.9)
Pre-procedural	44 (88.0)	43 (79.6)
At discharge	48 (96.0)	48 (88.9)
30 days	47 (94.0)	47 (87.0)
3 months	47 (94.0)	47 (87.0)
6 months	44 (88.0)	44 (83.0)*
ß-blocker		
Screening	38 (76.0)	42 (77.8)
Pre-procedural	/	/
At discharge	36 (72.0)	43 (79.6)
30 days	36 (72.0)	41 (75.9)
3 months	36 (72.0)	41 (75.9)
6 months	37 (74.0)	38 (71.7)*
Nitrates		
Screening	28 (56.0)	33 (61.1)
Pre-procedural	/	/
At discharge	29 (58.0)	33 (61.1)
30 days	28 (56.0)	35 (64.8)
3 months	31 (62.0)	38 (70.4)
6 months	31 (62.0)	37 (69.8)*
Statins		
Screening	46 (92.0)	47 (87.0)

Subjects Taking Medication – n (%)	Reducer N=50	Control N=54*
Pre-procedural	/	/
At discharge	44 (88.0)	50 (92.6)
30 days	43 (86.0)	50 (92.6)
3 months	44 (88.0)	50 (92.6)
6 months	44 (88.0)	49 (92.5)*
Ca++ Antagonists		
Screening	27 (54.0)	28 (51.9)
Pre-procedural	/	/
At discharge	26 (52.0)	25 (46.3)
30 days	26 (52.0)	26 (48.1)
3 months	26 (52.0)	27 (50.0)
6 months	28 (56.0)	27 (50.9)*

* Due to one subject death in the Control group, N=53 (Control group) and N=103 (all subjects) at the 6-month time point.

10.2 Adverse Events

10.2.1 Adverse Event Timing

Table 36 shows the timing of post-procedure adverse events.

Table 36. Adverse Events Summary – by Time of Event and Number of Events

	Reducer N=76	Control N=93
Prior to Discharge – n (%)		
Any adverse events	7 (9.2)	3 (3.2)
Serious adverse events	0 (0)	0 (0)
Deaths	0 (0)	0 (0)
Discharge to 30-Day Follow-Up* – n (%)		
Any adverse events	16 (21.1)	27 (29.0)
Serious adverse events	3 (3.9)	2 (2.2)
Deaths	0 (0)	0 (0)
30-Day to 3-Month Follow-Up – n (%)		
Any adverse events	22 (28.9)	21 (22.6)
Serious adverse events	1 (1.3)	4 (4.3)
Deaths	0 (0)	0 (0)
3-Month to 6-Month Follow-Up – n (%)		
Any adverse events	31 (40.8)	42 (45.2)
Serious adverse events	6 (7.9)	18 (19.4)
Deaths	0 (0)	1 (1.1)
6-Month to 12-Month Follow-Up – n (%)**		
Any adverse events	0 (0)	0 (0)
Serious adverse events	0 (0)	0 (0)

	Reducer N=76	Control N=93
Deaths	0 (0)	0 (0)

* Note: the NSTEMI in subject (b) (see Section 10.2.3) was considered to have occurred prior to the 30-day follow-up by the Investigator as the event happened when the subject was officially discharged; the subject had to be re-admitted by referral to the emergency room.

** Only the subjects from site 05 in Denmark (N=4) had a 12-month follow-up visit.

10.2.2 Adverse Events by Severity (Table 37)

The majority of AEs were characterized as mild (52.1%) or moderate (38.5%). Adverse Events were balanced between the treatment groups both by number of events and by number of subjects, with the exception that the Control group had a greater proportion of severe events (7.9% Reducer, 10.8% Control) and SAEs (13.2% Reducer, 25.8% Control).

Table 37. Adverse Events Severity

	Reducer	Control
By Number of Events – n (%)	**N=76**	**N=93**
Mild	40 (52.6)	48 (51.6)
Moderate	30 (39.5)	35 (37.6)
Severe	6 (7.9)	10 (10.8)
SAEs	10 (13.2)	24 (25.8)
By Number of Subjects – n (%)	**N=50**	**N=54**
Mild	21 (42.0)	23 (42.6)
Moderate	18 (36.0)	21 (38.9)
Severe	4 (8.0)	6 (11.1)

10.2.3 Periprocedural Events

Periprocedural SAEs were assessed in both the Reducer and Control groups. In the Reducer group, a periprocedural SAE was defined as a composite of death, MI, cardiac tamponade, clinically-driven re-dilation of a failed Reducer, life-threatening arrhythmias (VT or VF), and respiratory failure through 30 days post-procedure, as adjudicated by the CEC. There were 2 peri-procedural non-STEMIs in the Reducer group In the Control group, a periprocedural SAE was defined as a composite of death, MI, cardiac tamponade, life-threatening arrhythmias (VT or VF), and respiratory failure through 30 days post-procedure, as adjudicated by the CEC. There were no peri-sham procedural SAEs in the Control group.

Table 38. Periprocedural Serious Adverse Events

Adverse Event	Reducer N=50	Control N=54
Death	0 (0%)	0 (0%)
Myocardial infarction – NSTEMI*	2 (4.0%)	0 (0%)
Cardiac tamponade	0 (0%)	0 (0%)

Adverse Event	Reducer N=50	Control N=54
Re-dilation of failed Reducer	0 (0%)	0 (0%)
Life-threatening arrhythmias	0 (0%)	0 (0%)
Respiratory failure	0 (0%)	0 (0%)

* Both periprocedural events occurred in the same subject (b) (6)

10.2.4 Major Adverse Events

Major Adverse Events were defined as a composite of cardiac death, major stroke, and MI in the Reducer and Control groups through hospital discharge and at 30-day, 3-month, and 6-month post-procedural evaluations.

Excluding the 2 periprocedural MIs listed above, there were 5 MAEs in 5 subjects, as adjudicated by the CEC (Table 39). There was one MI in the Reducer group, and 3 MIs and a cardiac death in the Control group. The Reducer group had a numerically lower incidence of MAEs (2.0%) compared with Control (7.7%). None of the five events occurring after 30 days post-procedure were attributed to the index procedure or investigational device (Table 40). Only one MI was considered by the CEC to be related to a study-specific assessment, as it occurred during the study-required DSE at the 6-month follow-up.

Table 39. Major Adverse Events Occurring after 30 Days Post-Procedure (Excluding the 2 Periprocedural MIs from Subject 2-016)

Adverse Event – n (%)	Reducer N=50	Control N=54
Cardiac death	0 (0)	1(1.9)
Major stroke	0 (0)	0 (0)
Myocardial infarction	1 (2.0)	3 (5.6)

Table 40. Details of Major Adverse Events Occurring after 30 Days Post-Procedure (Excluding the 2 Periprocedural MIs from Subject 2-016)

Subject	MedDRA Preferred Term	Verbatim Term	Procedure Date	Event Date	Time Post-Procedure (days)	CEC Adjudication
Reducer						
(b) (6)	Myocardial infarction	Myocardial infarction	28 Feb 2012	23 Jun 2012	116	Not related to procedure or investigational device
Control						
(b) (6)	Cardiac death	Multi-system failure	10 Oct 2012	5 Feb 2013	118	Not related to procedure or investigational device
(b) (6)	Myocardial infarction	Myocardial infarction	26 Oct 2011	4 Mar 2012	130	Not related to procedure or investigational device

Subject	MedDRA Preferred Term	Verbatim Term	Procedure Date	Event Date	Time Post-Procedure (days)	CEC Adjudication
(b) (6)	Acute coronary syndrome	Acute coronary syndrome	10 Apr 2012	20 Sep 2012	163	Not related to procedure or investigational device, but considered related to study specific test (6MFU Echo)
(b) (6)	Acute coronary syndrome	Acute coronary syndrome	18 Sep 2012	16 Feb 2013	148	Not related to procedure or investigational device

10.3 Exercise Tolerance Testing – ITT Population

Table 41. Exercise Tolerance Test (Changes from Baseline to 6MFU, Paired Data) – ITT

	Reducer	Control
Exercise Duration (seconds)	**N=37**	**N=40**
Baseline – mean (SD)	446.84 (197.65)	429.10 (186.30)
6-month follow-up – mean (SD)	511.53 (195.43)	433.40 (168.55)
Δ (baseline to 6MFU) – mean (SD)	64.68 (166.31)	4.30 (136.37)
% Δ (baseline to 6MFU)	**14.47%**	**1.00%**
Time to 1 mm ST Segment Depression	**N=7**	**N=6**
Baseline – mean (SD)	424.00 (95.25)	411.00 (121.80)
6-month follow-up – mean (SD)	500.29 (151.53)	444.83 (175.28)
Δ (baseline to 6MFU) – mean (SD)	76.29 (83.59)	33.83 (110.25)
% Δ (baseline to 6MFU)	**17.99%**	**8.23%**
Maximal ST Segment Depression (mm)	**N=15**	**N=13**
Baseline – mean (SD)	-1.07 (0.53)	-1.22 (0.70)
6-month follow-up – mean (SD)	-1.09 (0.63)	-0.89 (1.34)
Δ (baseline to 6MFU) – mean (SD)	-0.02 (0.53)	0.32 (0.93)
% Δ (baseline to 6MFU)	**1.86%**	**-26.58%**

Table 42. Exercise Tolerance Test (Changes from Baseline to 6MFU, LOCF) – ITT

	Reducer	Control
Exercise Duration (seconds)	**N=42**	**N=48**
Baseline – mean (SD)	441.29 (193.74)	463.67 (256.84)
6-month follow-up – mean (SD)	499.81 (194.32)	467.25 (245.68)
Δ (baseline to 6MFU) – mean (SD)	58.52 (161.26)	3.58 (125.81)
% Δ (baseline to 6MFU)	**13.26%**	**0.77%**
Time to 1 mm ST Segment Depression	**N=11**	**N=11**
Baseline – mean (SD)	384.82 (137.23)	437.09 (154.14)
6-month follow-up – mean (SD)	433.36 (184.98)	455.55 (180.40)
Δ (baseline to 6MFU) – mean (SD)	48.55 (79.83)	18.45 (87.21)
% Δ (baseline to 6MFU)	**12.62%**	**4.22%**

	Reducer	Control
Maximal ST Segment Depression (mm)	**N=19**	**N=18**
Baseline – mean (SD)	-1.14 (0.54)	-1.01 (0.82)
6-month follow-up – mean (SD)	-1.16 (0.62)	-0.77 (1.27)
Δ (baseline to 6MFU) – mean (SD)	-0.02 (0.48)	0.23 (0.82)
% Δ (baseline to 6MFU)	**1.40%**	**-22.77%**

10.4 Device Malfunctions

There were 62 devices prepared for use in the COSIRA study; 52 were used in subjects randomized to the Reducer group, and 10 were discarded due either to what the sponsor describes as a "device deficiency" (9) or device malfunction (1). The following tables summarize these malfunctions:

Table 43. Device Malfunctions

Device Malfunctions	Reducer Group (non-technical failures)
Operator mishandling	8
Reducer was moved on balloon while inspecting	4
Reducer needed to be snared	2
Tracking issues on wire	1
Reducer "snagged" on gauze prior to insertion	1
Non-operator issues	1
Thrombi present	1

Of the 50 subjects randomized to the Reducer group who were implanted, there was one device malfunction (2.0%): in one subject, the Reducer slipped on the balloon while advancing the undeployed device to the intended location for implantation.

10.5 Enrollment Distribution by Study Site

Table 44 shows the number of subjects who were enrolled and randomized at each site.

Table 44. Enrollment and Randomization

Site #	Hospital (Location)	Total Subjects Enrolled n (%)	Randomization	
			Control n (%)	Treatment n (%)
1	(b) (6)	31 (29.8%)	16 (30.8%)	15 (28.8%)
2		23 (22.1%)	11 (21.2%)	12 (23.1%)
3		5 (4.8%)	3 (5.8%)	2 (3.8%)
4		4 (3.8%)	2 (3.8%)	2 (3.8%)
5		4 (3.8%)	2 (3.8%)	2 (3.8%)
6		5 (4.8%)	2 (3.8%)	3 (5.8%)

Site #	Hospital (Location) (b) (6)	Total Subjects Enrolled n (%)	Randomization	
			Control n (%)	Treatment n (%)
7	[redacted]	14 (13.5%)	7 (13.5%)	7 (13.5%)
8		6 (5.8%)	3 (5.8%)	3 (5.8%)
9		4 (3.8%)	2 (3.8%)	2 (3.8%)
10		3 (2.9%)	2 (3.8%)	1 (1.9%)
11		5 (4.8%)	2 (3.8%)	3 (5.8%)
Total:		**104 (100%)**	**52 (100%)**	**52 (100%)**

11 Appendix B – Adjunctive Data Provided in the PMA

11.1 FIH Study Adjunctive Data

11.1.1 Study Design

A prospective, open-label, single-arm, multi-center, clinical investigation was conducted at three centers. Fifteen subjects meeting the inclusion/exclusion criteria were enrolled and were treated with the first generation Reducer. Follow up was conducted at 7 days, 30 days, 3 months, and 6 months post-procedure to evaluate changes in primary and secondary endpoints compared to baseline performance variables. Ethics Committee approval and signed Informed Consent forms were obtained prior to enrollment.

Fifteen subjects with documented refractory angina pectoris in the presence of coronary artery disease, proven myocardial ischemia, CCS functional class of III or IV, and ejection fraction (EF)>30% who were not candidates for revascularization procedures (PCI or CABG) were enrolled. All subjects had objective evidence of reversible myocardial ischemia of the left anterior descending (LAD) artery or left circumflex (LCX) artery territories of the left ventricle by thallium single-photon emission computed tomography (SPECT) and/or by dobutamine echocardiogram (echo). All were electively treated with the Reducer System.

11.1.2 Inclusion Criteria

Subjects were eligible for enrollment into the study if they met all of the following criteria:

- Symptomatic coronary artery disease with chronic refractory angina defined as Canadian Cardiovascular Society (CCS) class III or IV despite medical therapy for 30 days prior to screening
- Coronary artery disease that is either not amenable or at high risk for revascularization by coronary artery bypass grafting or by percutaneous coronary intervention
- Reversible ischemia of the left ventricular wall, as determined by myocardial perfusion scan, and/or by stress echo
- Left ventricular ejection fraction (LVEF) greater than 30%
- Age is >18 years
- Subject (or legally authorized representative) understands the nature of the procedure and provides written informed consent prior to enrollment
- Willing to comply with specified follow-up evaluation and can be contacted by telephone
- Male or non-pregnant female patient (Note: Females of child bearing potential must have a negative pregnancy test)

11.1.3 Exclusion Criteria

Subjects were not eligible for enrollment into the study if they met any of the following criteria:

- Currently enrolled in another investigational device or drug trial that has not completed the primary endpoint or that clinically interferes with the current study endpoints

- Has had a recent (within three months) myocardial infarction
- Has had a recent (within seven months) angioplasty or coronary artery bypass surgery
- Has severe arrhythmias, including chronic atrial fibrillation
- Has major co-morbid condition(s) that could limit his/her ability to participate in the study or to comply with follow-up requirements, or may impact the scientific integrity of the study
- Has severe chronic obstructive pulmonary disease (COPD) indicated by forced expiratory volume in one second that is less than 55 percent of the predicted value
- Has need for continued use of intravenous anti-anginal or diuretic medication
- Is unable to undergo thallium stress scintigraphy or stress echo test (exercise or pharmacologic)
- Has decompensated congestive heart failure (CHF)
- Has severe valvular heart disease
- Has intolerance to clopidogrel, aspirin or heparin
- Has a pacemaker or other electrodes in the coronary sinus
- Has AV nodal dysrhythmia and high degree AV block
- Has mean right atrial pressure >15 mmHg
- Underwent tricuspid valve replacement or repair
- Is suffering from any one of the following:
  - Hepatic insufficiency;
  - Thrombophlebitis or deep venous thrombosis;
  - Thrombocytopenia (platelets count < 100,000/mm3) pre-procedure;
  - Chronic renal failure (serum creatinine > 2 mg%, except individuals who are in chronic hemodialysis);
  - Receiving immunosuppressant therapy;
  - Leukopenia (leukocytes count < 3.5 x 109/liter);
  - Neutropenia (absolute neutrophil count < 1000/mm3) ≤ three days prior to enrollment;
  - Active peptic ulcer or active GI bleeding;
  - Bleeding diathesis or hypercoagulable state
- Has contraindication to required study medications
- Has known allergy to stainless steel
- Has known sensitivity to contrast medium that cannot be adequately controlled with premedication
- Has anomalous or abnormal coronary sinus as demonstrated by angiogram. Abnormality can be defined as:
  - Abnormal CS anatomy (tortuosity, aberrant branch, persistent left SVC, etc.); and
  - CS diameter at the site of planned Reducer implantation >12 mm
- Has reversible myocardial ischemia due to right coronary artery disease

A single Reducer was implanted in the coronary sinus and each subject was required to return to the study site for follow-up tests.

11.1.4 Endpoints

Descriptive safety endpoint: The safety endpoint was the absence of any major procedure-related adverse events (AEs) through six months post-implantation. A major procedure-related AE is defined as: death; myocardial infarction; perforation of the coronary sinus; total occlusion of the coronary sinus; thrombosis of the coronary sinus; or need for urgent dilation of the Reducer.

Secondary endpoints: The secondary endpoints were defined as follows:

- **Technical success**: The successful delivery and deployment of the Neovasc Reducer in the CS as assessed by angiography.
- **Effectiveness**: Clinical improvement in performance variables and angina score classified according to the Canadian Cardiovascular Society Classification (CCS) guidelines.

11.1.5 Demographics

The sponsor indicates that all subjects had evidence of reversible myocardial ischemia of the LAD or LCX territories of the left ventricle by thallium SPECT and/or by dobutamine echo. Subjects were 80% male with a mean age of 59 years. The majority (12 patients) were CCS class 3, with 1 CCS class 2 and 2 CCS class 4 subjects included. The patient population characteristics are presented in Table 45.

Table 45. FIH Study Subject Characteristics

Characteristic	N	%
Male	12	80%
Female	3	20%
Age (years at time of procedure)	37-79	Mean=59
S/P myocardial infarction	4	26%
S/P percutaneous coronary intervention	6	40%
S/P coronary artery bypass graft	3	20%
Hypertension	10	75%
Hyperlipidemia	5	33%
Diabetes	1	7%
Angina class		
• CCS 2	1	7%
• CCS 3	12	80%
• CCS 4	2	13%
Number of diseased vessels		
• 1	3	20%
• 2	6	40%
• 3	6	40%

11.1.6 Clinical Enrollment

Enrollment was conducted at three study locations (Table 46).

Table 46. Clinical Sites with Enrollment

Site #	Principal Investigator	Location
002	(b) (6)	[redacted]
003		
004		

11.1.7 Results

11.1.7.1 Descriptive Safety Endpoint

The descriptive safety endpoint was a composite major procedure-related AE rate from index procedure to six months follow up. There were no major procedure-related AEs (death, MI, perforation of the CS, occlusion of the CS, thrombosis of the CS, or need for urgent dilation of the Reducer) reported in this study

11.1.7.2 Secondary Safety Endpoint

The successful delivery and deployment of the Reducer in the CS as assessed by angiography was observed in 100% (15/15) subjects.

11.1.7.3 Secondary Effectiveness Result

The effectiveness was assessed based on clinical improvement in CCS scores as measured by the Seattle Angina Questionnaire (SAQ).

Table 47. FIH CCS Improvement from Baseline to 6 Months

Secondary Endpoint (CCS Classification)	Neovasc % (n/N)
Angina score (CCS classification)* improvement at six-month follow-up compared to baseline	85.7% (12/14)
Angina score (CCS classification)* remained constant at six-month follow-up compared to baseline	14.3% (2/14)
Angina score (CCS classification)* worsened at six- month follow-up compared to baseline	0% (0/14)

* According to composite scoring Seattle Angina Questionnaire.

Table 48. FIH CCS Class at Baseline Compared to 6-Month Follow Up

Secondary Endpoint	Neovasc % (n/N)
Average CCS* class at baseline	3.07±0.47**

Secondary Endpoint	Neovasc % (n/N)
Average CCS* class at six-month follow up	1.64±0.84**

* According to composite scoring Seattle Angina Questionnaire.

** Average class at baseline = 3.2 reported in tables, however patient (b) who underwent PCI was excluded from the efficacy analysis and was therefore removed from this analysis.

There was an average improvement of 1.43 CCS classes based upon the CCS mean value for the group. 12/14 (86%) patients show at least one functional CCS class improvement during the follow-up period.

Table 49. Seattle Angina Questionnaire (FIH Study)

	N	Mean	Standard Deviation	Min - Max
Baseline				
Physical limitation	14	36.90	18.39	8.33-66.67
Angina stability	15	31.67	22.09	0.00-50.00
Angina frequency	15	48.67	25.32	10.00-100.00
Treatment satisfaction	15	52.50	27.43	12.50-100.00
Quality of life	15	30.53	22.45	0.00-66.75
Three-month follow-up				
Physical limitation	15	62.13	30.46	8.33-97.22
Angina stability	14	69.64	29.71	0.00-100.00
Angina frequency	15	73.33	26.90	10.00-100.00
Treatment satisfaction	15	79.58	19.69	43.75-100.00
Quality of life	15	54.98	34.19	0.00-100.00
Six-month follow-up				
Physical limitation	12	69.56	40.24	0.00-100.00
Angina stability	15	50.00	18.90	0.00-75.00
Angina frequency	15	72.00	33.42	10.00-100.00
Treatment satisfaction	15	82.92	22.96	43.75-100.00
Quality of life	15	59.47	38.44	0.00-100.00

One patient included in the safety/feasibility analysis was excluded from the quality of life/angina score analysis as well as from the stress and perfusion test analyses. This patient continued to suffer from severe angina after implantation of the Reducer cardiac computed tomography (CT) angiography showed a diseased saphenous vein graft that was missed during the baseline coronary angiogram. The obstructive saphenous vein graft lesion was treated with a stent, and the patient's symptoms improved significantly. This event was classified as a SAE (not procedure related) as the condition was present in a vessel other than the target vessel (CS) and was unrelated to the Reducer procedure. Please see Section 11.1.7.5 for additional discussion regarding this event.

11.1.7.4 Other Measures of Effectiveness

11.1.7.4.1 ST-Segment Depression During Exercise Stress Test

Of the 11 subjects (73.3%) in whom electrocardiographic tracings at baseline and at six-month stress test were of good technical quality, transient ST-segment depression was documented during the baseline exercise stress test for nine of the 11 patients. At six-month follow-up, ST-segment depression was lower in six of these nine subjects, and was no longer present in two of the six subjects. One subject had a higher ST-segment depression at six months. The average ST-segment depression for the nine subjects was 2 mm at a mean heart rate of 117 beats/min at baseline and 1.22 mm at a mean heart rate of 124 beats/min at follow-up ($p = 0.047$). In nine of the 11 patients, exercise duration and peak heart rate increased at the six-month follow-up stress test, compared with baseline.

11.1.7.4.2 Dobutamine Echocardiography

In 13 of the 14 subjects, dobutamine echocardiography data were of good technical quality. In eight of these 13 subjects (61.5%) there was a medically significant improvement (a change of one score or more in at least two segments). The stress images at baseline and six months were compared (score of all 18 segments of stress dobutamine echocardiography images were summed and compared to baseline. The average score of all 18 segments was lower at six months (baseline = 5.08, six months = 1.08, difference 4.00; $p = 0.004$). As shown in Figure 10, for the remaining five subjects who did not show a medically significant improvement, three had a higher total score at six months (#5, #9, and #11) than at baseline and two had a lower score (#12, #13); the differences were relatively small, and all five had low baseline values.

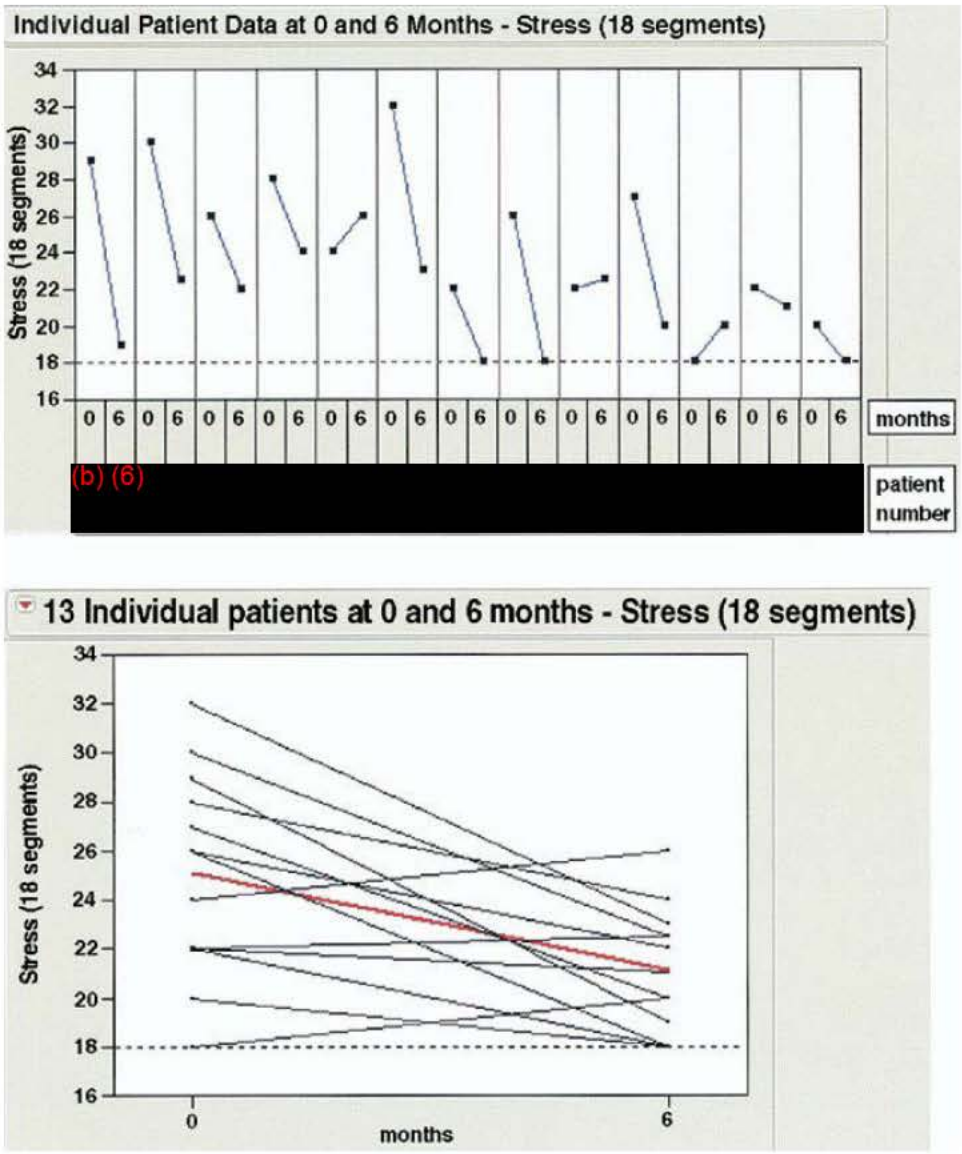

Figure 10. DSE Results at Baseline for FIH Subjects (a, top) and 6-Month Follow-Up (b, bottom) By Subject (n=13)

11.1.7.4.3 Thallium SPECT Perfusion Studies

In ten subjects (66.7%), SPECT images were of good technical quality at baseline and six months. In four of the ten subjects there was a medically significant reduction in the extent and/or severity of myocardial ischemia as measured by the total score. Among the remaining six subjects, the SPECT images were unchanged in five and worsened in one subject at six months. The average score for the group was 12.6 at baseline and 9.6 at six months, p = 0.042 (n=10).

11.1.7.5 Adverse Events

There were no major procedure-related AEs during the procedure or throughout the follow-up periods as defined by the clinical protocol (death; myocardial infarction (MI); perforation of the coronary sinus; total occlusion of the coronary sinus; need for urgent dilatation of the Neovasc

Reducer). Neovasc determined one of the AEs reported as "not serious", based on the medical evaluation and clinical assessment described in the clinical protocol, was congruent with the current company interpretation of a reportable incident for clinical investigations. This information is summarized in Table 50.

Table 50. Adverse Events

Subject ID	Procedure/ Event Date	Type of Event	Event Description	Major Procedure - related AE*	Serious Y/N
(b) (6)	25-Nov-04/ 25-Nov-04	Reducer partially detached from balloon	Reducer partially detached from balloon, not implanted, removed	No	No
(b) (6)	02-Feb-05/ 02-Feb-05	Reducer partially detached from balloon	Reducer partially detached from balloon, not implanted, removed	No	No
(b) (6)	08-Jun-05/ 12-Oct-05	PCI	Admitted with severe disabling angina; underwent repeat coronary angiography; subsequently underwent ptca+stent to SVG to RCA and stent to LCX and OM	No	Yes
(b) (6)	22-Mar-05/ 22-Mar-05	Reducer migrated into right pulmonary artery	Stent migrated 2-3mm backwards on balloon during insertion – stent was inflated more proximal to the CS ostium (diameter larger), wire position was lost, and the stent migrated to the RA and then to the PA	No	Yes**

* Reducer thrombosis, CS occlusion, CS perforation, need for urgent dilatation of the Reducer.
** Modified from No to Yes, see explanation below.

There were two occurrences of the stent moving on the balloon (subject IDs (b) (6) and (b) (6)) The balloon (with Reducer) was placed into the sheath and advanced toward the CS. During fluoroscopic guidance the investigator observed the Reducer was moving on the balloon catheter. Eventually, the Reducer became detached from the balloon catheter. However, wire position was maintained, and the Reducer was retrieved with a snare device. Another Reducer was then hand crimped on the balloon catheter and successfully implanted in the subject.

One subject (ID (b) (6)) was excluded from the effectiveness results prior to the six-month evaluation. The subject experienced chest pains and subsequently underwent an angiogram and angioplasty of a saphenous vein graft (SVG). It was noted that at baseline angiography the SVG was not evaluated. It could not be visualized because there were no makers on the graft, nor was a surgical report available at the time. Evaluation of the Reducer effectiveness was not possible for this subject because of the additional complications of the SVG intervention, therefore only the safety results of the implant procedure are included in this report.

There was one incident (ID (b) (6)) of Reducer migration post-implantation. The Reducer was noted to have moved during insertion under fluoroscopy, but the device was subsequently inflated. As a result, the position of the deployed Reducer device was more proximal, (close to

the CS ostium) than desired. Before a (post-dilatation) balloon inflation could be performed, the balloon catheter and the guidewire were removed from the subject. The dislodged Reducer then migrated from the CS into the right atrium (RA), through the right ventricle and out to a distal position in the pulmonary artery (PA) in the lower lobe of the right lung. A decision was made by the site medical team not to retrieve the dislodged device from the PA. Subsequently, a second Neovasc Reducer was implanted in the CS without complications.

11.1.7.6 Protocol Deviations

After completion of the data collection for all follow-up periods, a review was completed by the sponsor, and they determined that one subject who had been admitted to the study had CCS class II angina and not class III as had originally been assessed by the site. In this case the procedure had already been completed and data for this subject was to be included.

With respect to long term follow-up on FIH subjects, please refer to the publication by Parikh et al. (2018) in Appendix C.

11.2 REDUCER-I Study

11.2.1 Enrollment and Demographics

Table 51. Study Enrollment and Exit Summary

Enrollment/Exit Detail	All Subjects N	Arm 1 N	Arm 2 N	Arm 3 N
Subjects Enrolled (consented)	241	191	11	39
Subject Exited from Study (Discontinued)	59	30	11	18
Subject completed study	23	0	11	12
Screen failures[1]	14	11	0	2
Subject withdrawal consent post procedure[2]	5	4	0	0
Subject lost to follow-up	1	0	0	1
Death[3]	13	10	0	3
Other[4]	5	5	0	0
Current active subjects as of March 12, 2020, N (%)	**182 (75.5%)**	161 (84.3%)	0 (0.0%)	21 (53.8%)

1 Screen failure subjects = Subjects who did not meet eligibility requirements at the time of screening, or angiographic requirements at the time of the procedure: (b) (6) , (b) (6) , (b) (6) , (b) (6) , (b) (6) , (b) (6) , (b) (6) , (b) (6) , (b) (6) , (b) (6) , (b) (6) , (b) (6) , (b) (6) , (b) (6)

2 Subjects withdrew post procedure for personal reasons unrelated to the device or procedure.

3 Ten deaths were adjudicated as not device or procedure related; three have not yet been adjudicated

4 "Other" exited subjects

(b) (6) : Arm 1 subject angiographic exclusion, CS diameter too small

(b) (6) Arm 1 subject procedure aborted due to CS dissection before the Reducer was introduced

(b) (6) and (b) (6) Arm 1 subjects were withdrawn after the implant due to not completing required baseline assessments

(b) (6) Arm 1 subject was withdrawn after the implant before the 24-month visit. A query requesting additional information was outstanding at the time of the data cut for this report

Table 52. Subject Demographics and Medical History

Characteristic[1]	Overall (N=241)	Arm 1 (Prospective) (N=191)	Arm 2[3,4] (COSIRA Follow-up) (N=11)	Arm 3[3] (CE Mark) (N=39)
Age - years	68.1 ± 9.6 (241)	68.5 ± 9.6 (191)	63.2 ± 9.0 (11)	67.9 ± 9.9 (39)
Male sex	80.1% (193/241)	81.7% (156/191)	90.9% (10/11)	69.2% (27/39)
Previous myocardial infarction	51.0% (122/239)	51.3% (97/189)	54.5% (6/11)	48.7% (19/39)
Previous CABG	79.1% (189/239)	79.4% (150/189)	72.7% (8/11)	79.5% (31/39)
Previous PCI	70.7% (189/239)	71.4% (135/189)	54.5% (6/11)	71.8% (28/39)
Hypercholesterolemia	87.0% (208/239)	85.7% (162/189)	100.0% (11/11)	89.7% (35/39)
Diabetes mellitus	44.8% (107/239)	43.9% (83/189)	36.4% (4/11)	51.3% (20/39)
Hypertension	82.4% (197/239)	81.5% (154/189)	100.0% (11/11)	82.1% (32/39)
Current or previous smoking	61.5% (147/239)	63.0% (119/189)	63.6% (7/11)	53.8% (21/39)
CCS Angina Class				
I	0.9% (2/231)	0.0% (0/188)	0.0% (0/11)	6.3% (2/32)[5]
II	28.6% (66/231)	31.9% (60/188)	0.0% (0/11)	18.8% (6/32)
III	63.2% (146/231)	62.2% (117/188)	81.8% (9/11)	62.5% (20/32)
IV	7.4% (17/231)	5.9% (11/188)	18.2% (2/11)	12.5% (4/32)
Anginal Medication				
Antianginal Drugs	68.7% (158/230)	69.1% (132/191)	No data	66.7% (26/39)
Beta-Blockers (Beta-Adrenergic Blocking Agents)	37.8% (87/230)	38.7% (74/191)	No data	33.3% (13/39)
Calcium Channel Blocker (CCB)	19.1% (44/230)	18.3% (35/191)	No data	23.1% (9/39)
Vasodilators	32.6% (75/230)	33.0% (63/191)	No data	30.8% (12/39)
Number of Antianginal Medications[2]				
0	10.0% (23/230)	9.4% (18/191)	No data	12.8% (5/39)
1	21.3% (49/230)	20.4% (39/191)	No data	25.6% (10/39)
2	26.5% (61/230)	26.7% (51/191)	No data	25.6% (10/39)
3	26.5% (61/230)	27.7% (53/191)	No data	20.5% (8/39)
>3	15.7% (36/230)	15.7 (30/191)	No data	15.4% (6/39)

[1] Categorical data are presented as % (n/N) and continuous data are presented as mean ± SD (N)

[2] Including Antianginal Drugs, Beta-Blockers (Beta-Adrenergic Blocking Agents), Calcium Channel Blocker (CCB), Vasodilators

[3] Some COSIRA (Arm 2) and Arm 3 subjects may not have site visits at all visit intervals during the time period between the end of the COSIRA, or after their CE mark implant, and the time they enrolled into the REDUCER-I study. Therefore, retrospective data is not available at all timepoints

[4] Baseline medications in COSIRA were not categorized in the same way as REDUCER-I

[5] The REDUCER-I protocol sections 8.4.2.1 and 8.5.1 recognizes that due to of the retrospective nature of data collection for Arm 2 and Arm 3 subjects, existing data would be collected if it were available. The N reflects the data not available retrospectively

11.2.2 Effectiveness Results

Table 53. Change in Seattle Angina Questionnaire (SAQ) over Time – Arm 1 (Paired Data)

Time Interval	Data Values	Physical Limitations	Anginal Stability	Anginal Frequency	Treatment Satisfaction	Quality of Life
Baseline	**Baseline Overall**	54.0 ± 24.2 (177)	41.4 ± 23.5 (180)	51.7 ± 27.3 (180)	79.2 ± 18.6 (180)	37.4 ± 22.6 (180)
6 Month	**Post Baseline**	67.4 ± 25.4 (133)	58.2 ± 25.1 (144)	72.4 ± 27.3 (144)	85.6 ± 16.7 (144)	62.2 ± 25.6 (144)
	Change from baseline	12.2 ± 23.0 (133)	15.5 ± 34.9 (144)	19.3 ± 28.1 (144)	6.2 ± 17.4 (144)	25.6 ± 26.9 (144)
	% Δ from baseline	35.9 ± 72.1 (133)	46.6 ± 96.7 (128)	77.7 ± 146.8 (141)	13.3 ± 34.9 (144)	122.7 ±191.8 (136)
12 Month	**Post Baseline**	67.8 ± 24.6 (103)	57.3 ± 27.1 (113)	71.9 ± 26.9 (113)	88.9 ± 15.8 (113)	65.6 ± 26.0 (113)
	Change from baseline	13.5 ± 22.2 (103)	14.4 ± 35.2 (113)	17.7 ± 28.1 (113)	8.9 ± 17.5 (113)	28.7 ± 27.0 (113)
	% Δ from baseline	39.7 ± 70.5 (103)	36.1 ± 84.2 (101)	69.6 ±134.5 (112)	15.1 ± 29.3 (113)	131.8 ± 200.9 (105)
24 Month	**Post Baseline**	59.0 ± 27.1 (62)	51.8 ± 22.8 (69)	69.9 ± 29.9 (69)	85.0 ± 18.7 (69)	62.7 ± 28.1 (69)
	Change from baseline	7.1 ± 28.8 (62)	8.7 ± 28.1 (69)	22.2 ± 28.6 (69)	5.6 ± 20.5 (69)	28.3 ± 25.8 (69)
	% Δ from baseline	27.8 ± 80.3 (62)	19.4 ± 59.0 (61)	97.9 ± 175.4 (68)	11.4 ± 35.5 (69)	145.6 ± 217.0 (64)
36 Month	**Post Baseline**	56.3 ± 32.4 (16)	46.1 ± 15.1 (19)	54.2 ± 33.7 (19)	83.9 ± 15.8 (19)	59.2 ± 29.4 (19)
	Change from baseline	18.2 ± 36.1 (16)	5.3 ± 25.8 (19)	19.5 ± 34.9 (19)	5.3 ± 20.1 (19)	25.9 ± 22.5 (19)
	% Δ from baseline	158.1 ± 431.1 (16)	11.8 ± 51.6 (17)	135.1 ± 244.6 (18)	11.8 ± 34.3 (19)	133.4 ± 206.0 (17)

Continuous data are presented as mean ± SD (N)

Table 54. Mean CCS Grade Change Over Time – All Arms (Paired Data)

CCS Grade[1]	Baseline	6 Month	12 Month	24 Month	36 Month	48 Month	60 Month
Grade I	0.9% (2/220)	37.2% (68/183)	43.4% (63/145)	39.0% (41/105)	29.4% (15/51)	45.2% (14/31)	40.9% (9/22)
Grade II	29.1% (64/220)	45.9% (84/183)	41.4% (60/145)	45.7% (48/105)	56.9% (29/51)	45.2% (14/31)	40.9% (9/22)
Grade III	63.6% (140/220)	15.8% (29/183)	13.8% (20/145)	15.2% (16/105)	13.7% (7/51)	3.2% (1/31)	9.1% (2/22)
Grade IV	6.4% (14/220)	1.1% (2/183)	1.4% (2/145)	0.0% (0/105)	0.0% (0/51)	6.5% (2/31)	9.1% (2/22)
Mean CCS Grade	**2.8** ± 0.6 (220)	**1.8** ± 0.7 (183)	**1.7** ± 0.7 (145)	**1.8** ± 0.7 (105)	**1.8** ± 0.6 (51)	**1.7** ± 0.8 (31)	**1.9** ± 0.9 (22)

CCS Grade[1]	Baseline	6 Month	12 Month	24 Month	36 Month	48 Month	60 Month
Mean change in CCS grade (from baseline to timepoint)	-	-0.9 ± 0.8 (181)	-1.0 ± 0.8 (140)	-1.1 ± 0.7 (98)	-1.0 ± 0.8 (44)	-1.3 ± 0.7 (26)	-1.2 ± 0.7 (20)

[1] Categorical data are presented as % (n/N) and continuous data are presented as mean ± SD (N)
* Note: Denominators that do not match "Overall" reflect incomplete data entry or missing data in the case report form at the time of this report

Table 55. Improvement in CCS Grade from Baseline Over Time – All Arms (Paired Data)

CCS Grade Change from Baseline[1]	6 Month	12 Month	24 Month	36 Month	48 Month	60 Month
Worsening from Baseline	2.2% (4/181)	1.4% (2/140)	1.0% (1/98)	0.0% (0/44)	0.0% (0/26)	0.0% (0/20)
No Change from Baseline	28.2% (51/181)	24.3% (34/140)	17.3% (17/98)	29.5% (13/44)	15.4% (4/26)	20.0% (4/20)
≥ 1 Grade Improvement	69.6% (126/181)	74.3% (104/140)	81.6% (80/98)	70.5% (31/44)	84.6% (22/26)	80.0% (16/20)
≥ 2 Grade Improvement	24.3% (44/181)	25.7% (36/140)	30.6% (30/98)	34.1% (15/44)	46.2% (12/26)	35.0% (7/20)
≥ 3 Grade Improvement	0.6% (1/181)	0.7% (1/140)	0.0% (0/98)	0.0% (0/44)	0.0% (0/26)	0.0% (0/20)

[1] Categorical data are presented as % (n/N).

12 Appendix C – Engineering, Biocompatibility, Sterilization, and Shelf-Life Testing

12.1 Design Verification and Validation Testing

Table 56 shows the design verification bench testing performed on the Neovasc Reducer System. The device met all established acceptance criteria.

Table 56. Neovasc Reducer System Bench Testing

Test	Test Method Description	Results
Reducer Material Characterization		
Material Composition	To identify material used in the construction of the Reducer.	Pass
Mechanical Properties (raw materials)	To define the minimum mechanical properties of the 316L SS (raw material) used to manufacture the Reducer.	Pass
Mechanical Properties (post processing)	To define the minimum mechanical properties of the 316L SS (post processing) used to manufacture the Reducer.	Pass
Corrosion Resistance	To determine resistance to pitting corrosion of the Reducer.	Pass
Reducer Dimensional and Functional Attributes		
Dimensional Verification	To inspect the dimensional properties of the Reducer.	Pass
Percent Surface Area	To determine the surface coverage of the Reducer in the vessel.	Pass
Foreshortening	To determine the foreshortening of the Reducer.	Pass
Mechanical Recoil	To determine the amount of elastic recoil of the Reducer after deployment.	Pass
Device Integrity	To determine the ability of the Reducer to resist damage during delivery and deployment.	Pass
Radial Stiffness/Strength	To determine the deformation characteristics of the stent while a radial load was applied.	N/A
Stress/Strain Analysis	To determine the stresses to the Reducer during delivery, deployment, and cyclical loading conditions.	N/A
Fatigue Analysis	To analyze the stresses to the Reducer during delivery, deployment, and cyclical loading conditions via use of the Goodman diagram of safety factor.	N/A
Accelerated Durability Testing	To determine the long-term integrity of the Reducer under cyclical loading conditions.	Pass
Particulate Evaluation	To evaluate the particulate generated during simulated use of the Reducer System.	N/A
MRI safety and compatibility	To evaluate the Reducer for Magnetic Resonance (MR) compatibility.	Pass
Radiopacity	To evaluate the visibility of the Reducer during clinical use.	Pass
Reducer Delivery System Dimensional and Functional Attributes		
Dimensional Verification	To inspect the physical and dimensional properties of the Reducer Delivery System.	Pass

Test	Test Method Description	Results
Delivery, Deployment, and Retraction	To evaluate the performance of the Delivery System to reliably deliver the Reducer to the intended location.	Pass
Balloon Rated Burst Pressure	To determine the rated burst pressure (RBP) of the balloon when used as intended.	Pass
Balloon Fatigue	To determine the ability of the balloon to withstand repeated inflation/ deflation cycles.	Pass
Balloon Compliance	To determine the relationship between the Reducer diameter and the balloon inflation pressure.	Pass
Balloon Inflation and Deflation Time	To determine the balloon inflation and deflation time.	Pass
Catheter Bond Strength/Tip Pull Test	To determine the strength of the bonds of the delivery system.	Pass
Flexibility and Kink Test	To evaluate the flexibility and resistance to kink of the delivery system.	Pass
Torque Strength	To demonstrate that the delivery system can withstand torsional forces that are typical of clinical use.	Pass
Device Securement	To determine the force that will dislodge the Reducer from the delivery system.	Pass
Freedom from air leak	To determine that the bonds of the delivery system do not allow leakage of air into the hub assembly.	Pass

12.2 Biocompatibility

Biocompatibility testing of the sterile finished Reducer System was performed in accordance with BS EN ISO 10993-1, Biological Evaluation of Medical Devices – Part 1: Evaluation and Testing (Table 57). The device passed all established acceptance criteria.

Table 57. Reducer Implant Biocompatibility

Test	Purpose	Reducer	Balloon Catheter	Reducer System	Results
Cytotoxicity *ISO 10993-5*	To determine potential for cytotoxicity of the test article extract	X	X	X	Non-cytotoxic
Sensitization *ISO 10993-10*	To evaluate the allergenic potential or potential for sensitization of the test article extracts	X	X	X	Non-sensitizing
Irritation *ISO 10993-10*	To screen test article extracts for potential to produce irritation	X	X	X	Non-irritant

Test	Purpose	Reducer	Balloon Catheter	Reducer System	Results
Systemic Toxicity *ISO 10993-11*	To screen test article extracts for potential systemic toxic effects	X	X	X	Non-toxic
Hemocompatibility *ISO 10993-4*	To assess the potential hemolytic activity of the test article	X	X	X	Non-hemolytic
Material Mediated Pyrogenicity *ISO 10993-11*	To evaluate the potential of the test article extract to produce a pyrogenic response	X	X	X	Non-pyrogenic
Implantation *ISO 10993-6*	To determine the local tissue effects after test article implantation	X	n/a	n/a	Non-irritant
Chemical Characterization and Toxicological Risk Assessment					
Gas chromatography–mass spectrometry (GC-MS); Ultra-Performance Liquid chromatography– mass spectrometry (UPLC-MS); Inductively coupled plasma- mass spectrometry (ICP-MS); Ion Chromatography (IC), and Head Space GC-MS. (ISO 10993-18)	To identify possible volatile, semi- volatile and nonvolatile substances released from the test article via multiple instrumental methods and the subsequent toxicological evaluation of these substances.	X	n/a	n/a	Extractables / leachables not of toxico-logical concern for applicable endpoints

13 Appendix D – COSIRA-II Protocol Synopsis

Title:	COSIRA-II
Trial Objective:	To demonstrate the safety and effectiveness of the Reducer system for treatment of patients with refractory angina pectoris treated with maximally tolerated guideline-directed medical therapy who demonstrate objective evidence of reversible myocardial ischemia in the distribution of the left coronary artery and who are deemed unsuitable for revascularization.
Device Name:	Neovasc Reducer™ System (Reducer)
Indication for Use:	The Reducer is intended for patients with refractory angina pectoris despite guideline-directed medical therapy, who are unsuitable for revascularization by coronary artery bypass grafting or by percutaneous coronary intervention.
Trial Design:	A multicenter, randomized (1:1 ratio), double-blinded, sham- controlled clinical trial. Participants meeting all clinical and laboratory entry screening criteria will undergo right atrial pressure measurement with angiography of the coronary sinus to determine final eligibility, immediately after which eligible patients will be randomized 1:1 to: **Arm 1 (Treatment Arm)**: Implantation of the Reducer device **Arm 2 (Sham-control Arm)**: Control (no device implantation) Participants and those performing follow-up assessments (including physicians, research coordinators, and those administering exercise tests) will be blinded to the treatment assignment through the 12-month follow-up visit. Participants randomized to the sham-control arm will be allowed, but not required, to crossover to the treatment arm at the 12-month follow-up time point after completion of the study visit, provided they continue to satisfy all of the inclusion/exclusion criteria and are re-evaluated and approved by the Central Screening Eligibility Committee.
Number of Participants and Follow-up:	Approximately 380 participants at up to 35 investigational centers in North America will be randomized and followed at baseline, procedure, discharge, 30 days, 90 days, 6 months, 12 months and annually through 5 years. Each site will contribute no more than 20% of the total enrollment. It is anticipated that at least 40% of participants randomized will be from the United States. If requested, participants may be unblinded to their treatment assignment after completion of the 12-month follow-up visit.
Estimated Timeline:	First participant in: December 2017 Last participant in: December 2019 Last participant out: December 2024
Population:	Participants are those with coronary artery disease and refractory angina pectoris with Canadian Cardiovascular Society (CCS) grade III or IV angina, despite treatment with maximally tolerated guideline-directed medical therapy who demonstrate objective evidence of reversible myocardial ischemia in the distribution of the left coronary artery and who are deemed unsuitable for revascularization, as determined by the local heart team and confirmed by a Central Screening Eligibility Committee.

Title:	COSIRA-II
Inclusion/ Exclusion:	Clinical Inclusion Criteria: 1. Participant is older than 18 years of age 2. Symptomatic coronary artery disease (CAD) with ≥3 months of refractory angina pectoris classified as CCS Grade III or IV despite maximally tolerated guideline directed medical therapy (regimen stable for ≥2 months), with no intent to change the medical regimen for at least 12 months after randomization, as determined by the local heart team, and confirmed by a Central Screening Eligibility Committee 3. Participant has either no treatment options for revascularization by coronary artery bypass grafting or by percutaneous coronary intervention, or is otherwise unsuitable or high risk for revascularization as determined by the local heart team, and confirmed by a Central Screening Eligibility Committee 4. Evidence of either exercise or pharmacologically induced reversible ischemia by stress echo, nuclear study, PET, MRI or CT perfusion, in the distribution of the left coronary artery (LCA). Note: if the patient has evidence of ischemia in both the LCA and RCA distributions, the extent of ischemia must be greater in the LCA distribution 5. Functional limitation due to refractory angina as defined by a modified Bruce exercise tolerance test duration of greater than 3 minutes but less than 9 minutes a. Participant has ETT variability less than 20% between last two ETTs performed 6. Left ventricular ejection fraction (LVEF) ≥30% within the prior 12 months (must be reassessed after any intervening myocardial infarction); the most recent LVEF assessment is used as the qualifying test 7. Participant has provided their written informed consent 8. Participant is willing to comply with the specified follow-up evaluations Angiographic Inclusion Criteria 1. Coronary angiography performed within the prior 12 months demonstrating obstructive CAD in the distribution of the left coronary artery (visually assessed diameter stenosis of ≥70% in the epicardial left anterior descending (LAD) and/or left circumflex (LCX) coronary artery, or a fractional flow reserve (FFR) value of ≤0.80 or an iFR of ≤0.89 in a lesion with a visually assessed diameter stenosis of ≥50%) Clinical Exclusion Criteria: 1. Recent (within 30 days) troponin or CKMB positive acute coronary syndrome (ACS) (NSTEMI or STEMI). Note: participants with an elevated troponin or CKMB without ACS may still be enrolled 2. Recent (within six months) CABG or successful PCI. Note: patients in whom a PCI was attempted and was unsuccessful (e.g. a failed attempt to open a chronic total occlusion) may still be enrolled 3. Predominant manifestation of angina is dyspnea or other angina equivalent 4. Has contributory causes of angina – e.g., untreated hyperthyroidism, anemia (Hgb <10 g/dL), uncontrolled hypertension (systolic blood pressure >160 or

Title:	COSIRA-II
	diastolic blood pressure >100 despite medications), atrial fibrillation with rapid ventricular response (consistently >100 bpm despite medications), etc. 5. Decompensated heart failure (HF) or hospitalization due to HF during the three months prior to enrollment 6. Life threatening rhythm disorders or any rhythm disorders that would require future placement of an internal defibrillator and/or pacemaker 7. Severe chronic obstructive pulmonary disease (COPD) as indicated by a forced expiratory volume in one second that is less than 55% of the predicted value, or need for home daytime oxygen or oral steroids 8. Severe valvular heart disease (any valve) 9. Moderate or severe RV dysfunction by echocardiography 10. Pacemaker electrode/lead is present in the coronary sinus, or a Class I indication is present for cardiac resynchronization therapy according to ACCF/AHA/HRS Guidelines 11. Recent (within 6 months) implantation of a pacemaker or defibrillator with electrode in the right atrium 12. Prior tricuspid valve replacement or repair 13. Chronic severe renal failure (estimated creatinine clearance <30 mL/min/1.73m2 by the MDRD formula) or patients on chronic dialysis 14. Comorbidities limiting life expectancy to less than one year 15. Known allergy to stainless steel or nickel 16. Any clinical condition that might interfere with the trial protocol or the patient's ability to be compliant with the trial protocol (e.g., active alcohol or drug abuse, dementia, etc.) 17. Currently enrolled in another investigational device or drug trial that has not reached its primary endpoint or that might clinically interfere with the current trial endpoints or procedures 18. Pregnant or planning pregnancy within the next 12 months (women of reproductive potential must have a negative pregnancy test within 4 weeks of randomization) 19. Is a member of a vulnerable population, including prisoners, handicapped or mentally disabled persons, or economically or educationally disadvantaged persons <u>Angiographic/Hemodynamic Exclusion Criteria</u>: 1. Coronary anatomy amenable to revascularization of ischemic myocardial territory by either PCI or CABG with at least moderate likelihood of long-term alleviation of angina or angina equivalent symptoms, as per the assessment of the local heart team. Note: If a pathway to coronary revascularization is present which is reasonably low risk and reasonably likely to provide long-term symptom relief and the patient refuses the procedure, the patient is ineligible for randomization. 2. Mean right atrial pressure ≥15 mmHg assessed during the screening procedure for eligibility assessment and potential randomization

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	3. Suboptimal CS anatomy (e.g., excessive tortuosity, aberrant branch, congenital anomalies) 4. CS diameter at the proximal site of planned Reducer implantation <9.5 mm or >13 mm (measured 2-4 cm distal to the coronary sinus ostium)
Primary Endpoints	The primary endpoints will be assessed via a comparison between the Treatment and Sham-control arms. Effectiveness: Change in total exercise duration in modified Bruce treadmill exercise tolerance testing at 6 months post procedure compared to baseline in the Treatment arm compared to the Sham-control arm. Safety: The rate of occurrence of a composite of death, myocardial infarction (MI), pericardial effusion requiring surgical or percutaneous intervention, device embolization, or BARC 3 or 5 bleeding within 12 months post-procedure.

Secondary Endpoints	Secondary endpoints will be assessed in a comparison between the Treatment and Sham-control arms, utilizing a gatekeeping strategy to control the type I error rate.
	• Improvement by ≥1 CCS angina grade at 6 months
	• Change in Angina Stability domain score from the Seattle Angina Questionnaire (SAQ) at 6 months
	
	The following additional endpoints will not be formally tested:
	• Improvement by ≥1 and ≥2 CCS angina grades at 6 months, 12 months and annually post procedure compared to baseline
	• Angina frequency and burden at 6 months, 12 months and annually post procedure compared to baseline, assessed in an electronic diary over a 2 week period. Angina burden will be defined by the number, duration and severity of anginal episodes
	• Change in ETT parameters at 6 months and 12 months post procedure compared to baseline
	  • Time to level 3 angina
	  • Time to 1 mm ST-segment depression (in patients with qualifying baseline ECG)
	  • Double product at angina onset
	  • Maximal double product
	• Change in total exercise duration at 12 months compared to baseline
	• Total exercise duration at 6 and 12 months
	• Change in SAQ Score at 6 months, 12 months and annually post procedure compared to baseline
	• Number of hospitalizations, emergency department visits, and unplanned office visits due to angina at 6 months, 12 months and annually post procedure compared to baseline

14 Appendix E – Referenced Publications

Supportive data from the following published literature articles was provided in support of the COSIRA study: (Konigstein et al. 2018; Giannini, Baldetti, Ponticelli, et al. 2018; Gallone et al. 2019; Giannini, Baldetti, Konigstein, et al. 2018; Ponticelli et al. 2019; Parikh et al. 2018; Verheye et al. 2015). Copies of these articles are provided in the attached appendices.

FDA Comment: Some of the referenced articles may include individual center experiences within the setting of the COSIRA study.