NEOVASC REDUCER SYSTEM

SPONSOR EXECUTIVE SUMMARY

CIRCULATORY SYSTEM ADVISORY COMMITTEE

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AVAILABLE FOR PUBLIC RELEASE

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Abbreviation	Definition
6MWT	Six-Minute Walk Test
AE	Adverse event
CABG	Coronary artery bypass graft
CAD	Coronary artery disease
CCS	Canadian Cardiovascular Society
CEC	Clinical Events Committee
CHF	Congestive heart failure
COPD	Chronic obstructive pulmonary disease
CS	Coronary sinus
CT	Computed tomography
DSMB	Data safety monitoring board
ECG	Echocardiogram
ECHO	Echocardiography
EECP	Enhanced external counterpulsation
ETT	Exercise Tolerance Test
FDA	Food and Drug Administration
FIM	First in man
ITT	Intent-to-treat
LCA	Left Coronary Artery
LOCF	Last observation carried forward
LVEDP	Left ventricular end diastolic pressure
MACE	Major adverse cardiac events
MAE	Major adverse events
MI	Myocardial infarction
MRI	Magnetic resonance imaging
NNT	Number needed to treat
PCI	Percutaneous coronary intervention
PICSO	Pressure-Controlled Intermittent CS Occlusion System
PMA	Premarket Approval
PP	Per-protocol
SAE	Serious adverse event
SAQ	Seattle Angina Questionnaire
SOC	System organ class
UADE	Unanticipated adverse device effect
US	United States
WMSI	Wall Motion Score Index

1 SYNOPSIS

1.1 Introduction

Angina, refractory to medical and interventional therapies, is a disabling condition that severely impacts quality of life. The coronary sinus Reducer, developed by Neovasc, is a percutaneously implantable device, intended to relieve angina and improve quality of life of 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 Food and Drug Administration (FDA) granted Breakthrough Device Designation to the Reducer System in 2018, as it met the FDA's criteria for an expedited review of a medical device that provides for more effective treatment or diagnosis of life-threatening or irreversibly debilitating human disease or conditions, and represents a breakthrough technology for which no approved or cleared alternatives exist, offers significant advantages over existing approved or cleared alternatives, and availability is in the best interest of patients.

The Reducer System received CE Mark in 2011, while the COSIRA prospective, randomized, sham-controlled clinical trial was being conducted. Despite receiving the CE Mark, the Sponsor chose not to launch the product until the COSIRA study was completed and a final analysis was conducted, to ensure the safety of the treated patients. The COSIRA final report was completed in November 2014. The Sponsor began a very limited launch of the Reducer System in 2015 in 8 countries. The controlled launch was due to limited resources in addition to the challenges of obtaining reimbursement coverage for any new device. The Reducer System is now available in 18 countries at a limited number of centers. There have been more than 2,500 units distributed since 2015 outside of the United States (US).

The Sponsor submitted an Investigational Device Exemption (IDE) in September 2016, with approval obtained in November 2017. While the IDE was under review, in October 2017, FDA published the draft guidance on the Breakthrough Devices Program, which is intended to help patients have more timely access to medical devices by expediting development, assessment, and review, while preserving the statutory standards for premarket approval, consistent with the Agency's mission to protect and promote public health. While the IDE for the Reducer System was approved, it was clear it would be at least 5 years to complete the study and obtain regulatory approval to bring the Reducer technology to the patients in the US who have limited treatment options for their refractory angina. The Sponsor chose to seek Breakthrough Device Designation for the Reducer System which the FDA granted in October 2018, because the device had the potential to address an unmet need for these refractory angina patients. Since then, the Sponsor has had several interactive discussions with FDA. Following those meetings, the company filed the Premarket Approval (PMA) application for the Reducer System in late 2019.

1.2 Background and Unmet Need

Over the past few decades, improved treatment options have greatly increased the life expectancy of patients with obstructive CAD. However, despite these advances in medicine, up to 1.8 million Americans suffer from chronic refractory angina (Henry et al 2013; Henry et al 2014; Povsic et al 2015). A smaller subpopulation of between 26,000 to 52,000 patients have CCS class III or IV angina resulting in severe limitation in their ability to perform activities of daily living (Benck and Henry 2019). These "no option" patients need a novel, safe, and effective therapy.

Patients with angina experience pain, tightness, pressure, and discomfort in their chest due to coronary insufficiency in the presence of coronary artery disease (CAD). In addition to chest pain, patients may have discomfort in their shoulders, arms, neck, jaw, or back, or experience breathlessness, nausea, or epigastric pain.

The severity of angina, as measured by the Canadian Cardiovascular Society (CCS) grading scale shown in Table 1, can vary from pain only during strenuous or prolonged physical activity (class I) to pain with any activity, or even during rest (class IV). An improvement of ≥ 2 CCS classes represents a transformation from severe disability to mild or no physical limitation; however, even an improvement of 1 CCS class represents a clinically meaningful difference, which translates into improvement in quality of life and in everyday activity.

Table 1: Canadian Cardiovascular Society Scale for Grading Angina Pectoris

Class	Description
I	Ordinary physical activity does not cause angina, such as walking and climbing stairs. Angina with strenuous or rapid or prolonged exertion at work or recreation
II	Slight limitation of ordinary activity. Walking or climbing stairs rapidly, walking uphill, walking or stair climbing after meals, or in a cold, or in wind, or under emotional stress, or during the few hours after awakening. Walking more than 2 blocks on the level and climbing more than one flight of ordinary stairs at a normal pace and in normal conditions
III	Marked limitation of ordinary physical activity. Walking 1 or 2 blocks on the level and climbing one flight of stairs in normal conditions at a normal pace
IV	Inability to carry on any physical activity without discomfort, anginal syndrome may be present at rest

Source: (Campeau 1976)
https://www.ccs.ca/images/Guidelines/Guidelines_POS_Library/Ang_Gui_1976.pdf

Patients with angina are treated with medications (e.g., beta blockers, calcium channel antagonists, nitrates, ranolazine), PCI, or CABG. Lifestyle modifications, such as smoking cessation, weight loss, and stress reduction, are also recommended.

For patients who have exhausted standard treatment options, enhanced external counterpulsation (EECP) is an alternative treatment option, in which inflatable cuffs positioned on the lower limbs mechanically compress in time with a patient's heartbeat to increase blood flow to the heart. However, this treatment is inconvenient and time consuming.

Transmyocardial revascularization is another treatment option that was first approved over 20 years ago. A thoracotomy is performed to insert a laser to create channels in the targeted region of the heart with the goal of revascularizing ischemic tissue. This procedure is not widely available or accessible to many patients and requires hospitalization for several days, where Reducer is intended to be an outpatient procedure.

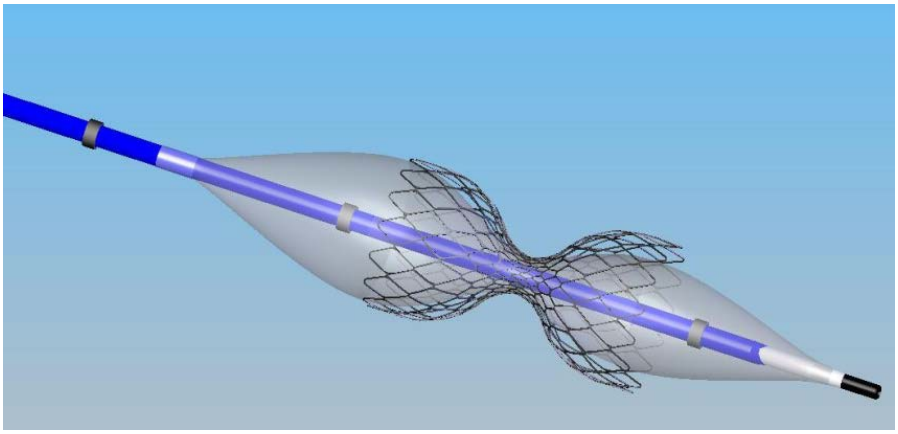
When current treatment options for refractory angina are exhausted with less than optimal results, there is still an unmet need in this patient population suffering from disabling refractory angina.

1.3 Device Description

The Reducer is a stainless-steel mesh device designed to create a focal narrowing in the lumen of the CS to generate a pressure gradient across it (Figure 1). The Reducer System comprises the Reducer device pre-mounted on a customized hourglass shaped balloon catheter. When inflated, the expanded balloon gives the metal mesh its final hourglass configuration.

The Reducer is implanted percutaneously via the right or left jugular vein into the CS. The semi-compliant delivery balloon is available in a single size, and the final expanded diameters are dependent on the inflation pressure. The Reducer is designed to fit the range of anatomies encountered in most patients, and it is compatible with CS diameters of 9.5–13 mm at the proximal implant site. The proximal and distal portions of the device are configured to different diameters, based on balloon expansion, allowing the device to conform to the tapered configuration of the anatomy of the CS, with the center of the device narrowing consistently 3 mm in diameter.

Figure 1: Neovasc Reducer System



Device Generations

The first generation of the Reducer (E15), which was provided unmounted and was hand crimped to a commercially available balloon catheter, was used in the first in man study. The second generation of the Reducer (B17W), used in the COSIRA study, was

pre-mounted on the delivery system to improve the usability of the system. The design of the devices is essentially the same with no change in the proximal and distal sections of the Reducer and only minor differences in the narrowed-neck region. Design and performance attributes for patency, flow characteristics, and fracture resistance were maintained in the design change and have been confirmed for both designs through clinical evaluation. More details on device generations are provided in Section 3.2.1.

1.4 Mechanism of Action

In the presence of myocardial ischemia, the Reducer is intended to improve perfusion to ischemic territories of the myocardium by forcing redistribution of blood from the less ischemic subepicardium to the more ischemic subendocardium, thus alleviating the symptoms of angina.

The Reducer is intended to establish a narrowing in the coronary sinus (CS), which is the final common vein draining the blood from the left ventricle of the heart. The design of the Reducer replicates key aspects of the Beck Procedure, which was a surgical treatment for patients with angina in the 1950s and 1960s before CABG surgery became mainstream (Beck and Leighninger 1955). Details on the Beck Procedure are provided in Section 3.3.3. Once implanted, the Reducer is intended to redistribute myocardial blood flow into ischemic areas of the subendocardial layers of the myocardium (Giannini et al 2019; Ido et al 2001; Konigstein et al 2018b). This redistribution of arterial blood is intended to reduce myocardial ischemia, resulting in relief of angina symptoms and improved CCS class.

The narrowing within the CS is intended to produce a pressure gradient across the device that is established 4–6 weeks after implantation, when the metal mesh should be covered by tissue ingrowth. After the device is implanted in the CS, the interaction between the metal struts and the vessel wall triggers a vascular reaction that leads to a hyperplastic response in the vessel wall, which cover the struts and fenestrations of the metal mesh. The central orifice of the device remains patent and becomes the sole path for blood flow through the CS.

1.5 Clinical Development Program

Preclinical Studies

Preclinical experiments preceded and set the basis for the clinical evaluation. Neovasc conducted preclinical animal studies on the Reducer System in the miniature swine model. The swine cardiovascular system is well understood and affords a similar size coronary sinus as humans but is different from humans in that the swine coronary sinus is contiguous with the left azygous vein (which drains the forelimbs).

The suite of studies performed by Neovasc included 2 pilot animal studies and one pivotal animal study spanning a preclinical research period of 7 years from 2002–2009 and included 52 animals. The individual study endpoints ranged from acute to six

months. 39 of the 52 animals were from two non-GLP feasibility studies from which FDA was provided with signed non-GLP study and pathology reports. The last 13 swine were subjects in a pivotal non-GLP study from which FDA was provided a final study report, source records containing data and information from implants and Reducer delivery system performance, and a pathology report containing macroscopic and microscopic data from the chronic animal subset of 7 animals.

This collection of studies included both pilot and pivotal work in ischemic and non-ischemic animal models. These experiments evaluated the safety, feasibility, and efficacy of Reducer implantation in a swine model with and without myocardial ischemia.

Data from the preclinical studies demonstrate 100% endothelialization of the luminal surface of the coronary sinus as early as 2 months. In addition, there were very low levels of inflammation at all time points and in all sections, and only rare incidents of uncovered stent struts. The totality of histopathology viewed provides clear evidence that cellular coverage is consistent with physiologic findings in non-GLP efficacy and safety studies. The mid-section strut coverage for the struts touching neointima of the lumen of the CS was predominantly complete with < 10% uncovered struts, although mid-section strut coverage is not necessary to achieve physiologic effect. The results also demonstrate that the device is reliably and easily implanted and provided a reasonable simulation of the human experience and outcome.

Overall, the preclinical studies demonstrate acceptable *in vivo* performance for: introduction of the Reducer; location of the device at the target anatomy (including some extension into the azygous vein, which is contiguous with the CS in swine); deployment of the device; angiographic visualization of the device, delivery system and all required steps in the procedure; and re-evaluation of the device at the appropriate follow-up procedures. In performance evaluations provided to FDA, among the 13 pigs in the pivotal non-GLP study, there were no instances of vessel tear or occlusion following the procedures in appropriately sized vessels as verified by angiography and histopathology. One coronary sinus tear occurred in an animal that was implanted contrary to the IFU in an overly small CS and caused a dissection, tamponade, and death.

Clinical Studies

The clinical development program for the Reducer began with the First in Man (FIM) Study, a prospective, open-label, multi-center feasibility study (Banai et al 2007). A total of 15 patients were enrolled in this study at 3 clinical sites (2 in India and 1 in Germany). Two additional prospective follow-up studies were conducted on the FIM cohort of patients: one study included 14 patients from the 3 study sites and evaluated them at 3 years post-implantation (Banai et al 2010), and the second study included 7 patients from 1 center and evaluated them at 12 years post-implantation (Parikh et al 2018).

The primary evidence for effectiveness and safety of the Reducer comes from the multi-center, prospective, sham-controlled, double-blind, randomized study, COSIRA, with supportive data from the long-term observational study, REDUCER-I, described below.

1.6 Effectiveness Findings

COSIRA was a prospective, multi-center, randomized, double-blind, sham-controlled study of 104 patients suffering from refractory disabling angina (CCS class III–IV), with objective evidence of reversible myocardial ischemia, who had limited treatment options and were thus referred to as “no option” patients. Patients were randomized 1:1 to the Reducer (n=52) and Control (n=52) arms. All patients (both study arms) underwent right-heart catheterization with right atrial pressure measurement, and CS selective angiography as the last screening test. The catheterization was followed by Reducer implantation only in the treatment group.

Although there was not a formal questionnaire to assess the effectiveness of the blind, several measures were taken to maintain the blinding. During the catheterization procedure, patients had headphones and listened to music and/or were given intravenous sedatives so they could not hear the conversation in the room. Aseptic draping was used to cover the patients’ faces so they could not see any of the activities taking place in the room. Revealing the treatment assignment (opening of the treatment randomization envelopes) occurred outside of the procedure room, and the content of the randomization envelope (i.e., “Reducer” or “No treatment”) was read silently and was never spoken. After the content of the envelope was seen by the operator, the physicians came back into the procedure room. The implanting physicians were instructed to behave similarly during both Reducer and sham implantations. Independent blinded physicians performed pre- and post-procedural CCS and SAQ assessments and dobutamine ECHO and ETT core laboratories were blinded to treatment assignments (more details are provided in Section 5.1.1.1).

Effectiveness measures included CCS class, Seattle Angina Questionnaire (SAQ) as a measure of quality of life and angina severity, dobutamine echocardiography (ECHO), and exercise tolerance test (ETT). A data safety monitoring board (DSMB) and Clinical Events Committee (CEC) served as oversight for the study.

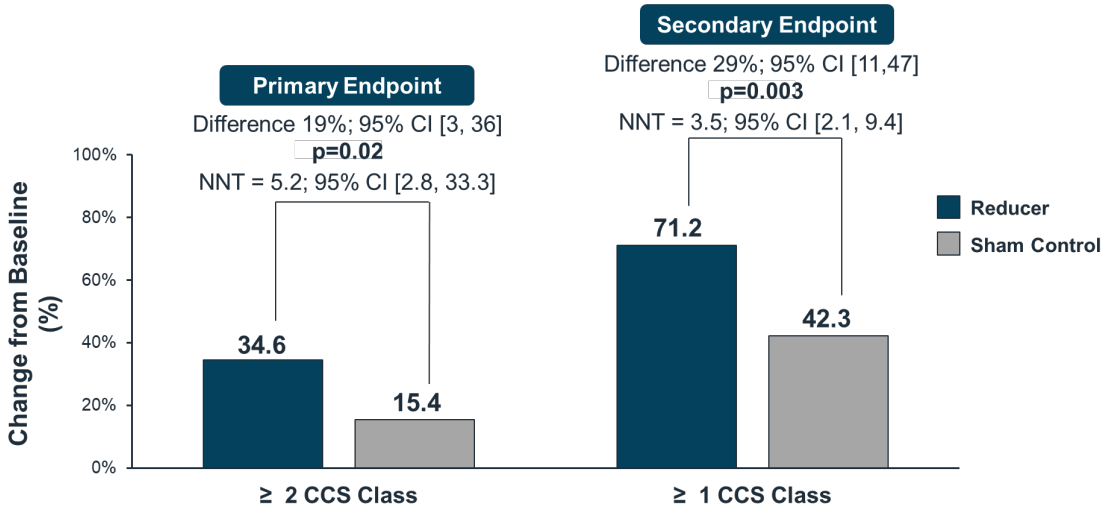
Patients in the study needed to have symptomatic CAD with chronic refractory angina pectoris classified as CCS class III or IV despite attempted optimal medical therapy for 30 days prior to screening. Patients had limited treatment options for revascularization by CABG or PCI and had to have evidence of reversible ischemia attributable to the left coronary arterial system by dobutamine ECHO. A full list of inclusion and exclusion criteria is provided in Appendix 10.1.

Baseline demographics and medical characteristics were well balanced between study arms. As seen in other studies of refractory angina (Jones et al 2019), patients were mostly male and predominantly White, with similar rates of diabetes and smoking in

both study arms. Rates of high cholesterol, hypertension, and previous myocardial infarction (MI) were also similar. Between 69% and 80% of patients in both groups had previous CABG surgery and/or PCI. Over 80% of patients in both study arms had a CCS class of III at baseline, and the remainder were class IV.

COSIRA met its primary effectiveness endpoint at 6 months: 34.6% of patients in the Reducer arm achieved a ≥ 2 CCS class improvement compared to 15.4% in the Control arm (p=0.024) (Figure 2). Additionally, more patients in the Reducer arm (71.2%) than the Control arm (42.3%) achieved a ≥ 1 CCS class improvement at 6 months (p=0.003), a secondary effectiveness endpoint.

Figure 2: COSIRA: ≥ 2 and ≥ 1 CCS Class Improvement at 6 Months



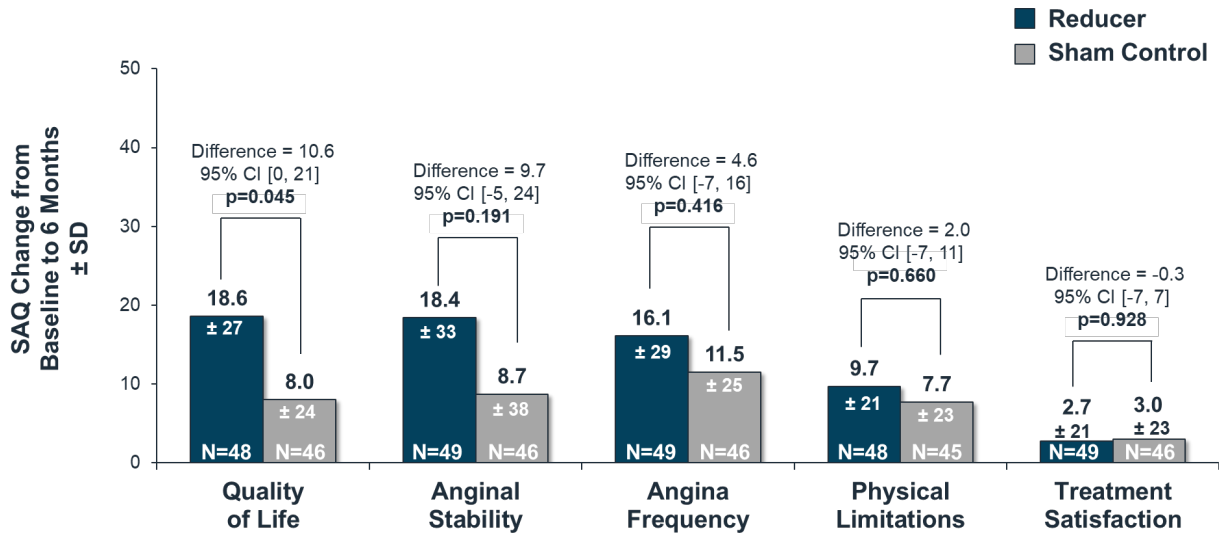
Note: Secondary endpoint analyses were not pre-specified and did not account for multiplicity.

Technical and procedural success were high in COSIRA. The Reducer was successfully implanted in 50/52 patients (96.2%), with 2 failures to implant due to anatomical variations as opposed to device design and/or performance. All 50 patients successfully implanted with the Reducer were also categorized as procedural successes.

Additional secondary effectiveness endpoints included the dobutamine ECHO wall motion score index (WMSI), SAQ, and ETT. It is important to note that the study was not statistically powered to establish improvement in angina by the secondary endpoint measures. Secondary endpoint analyses were not pre-specified and did not account for multiplicity. There were no statistically significant differences between study arms for the dobutamine ECHO WMSI. Modified LCA WMSI (stress) results showed a numeric decrease in WMSI (baseline to 6-month follow-up), with mean decreases of 0.18 (12.33%) and 0.09 (6.56%) (p=0.346) in the Reducer and Control groups, respectively. Quality of life domain scores on the SAQ were statistically significantly improved (p=0.048) in the Reducer group compared with the Control group (Figure 3); other domains of the SAQ did not show statistically significant differences between study arms. Although not statistically significant, patients in the Reducer arm had an increase

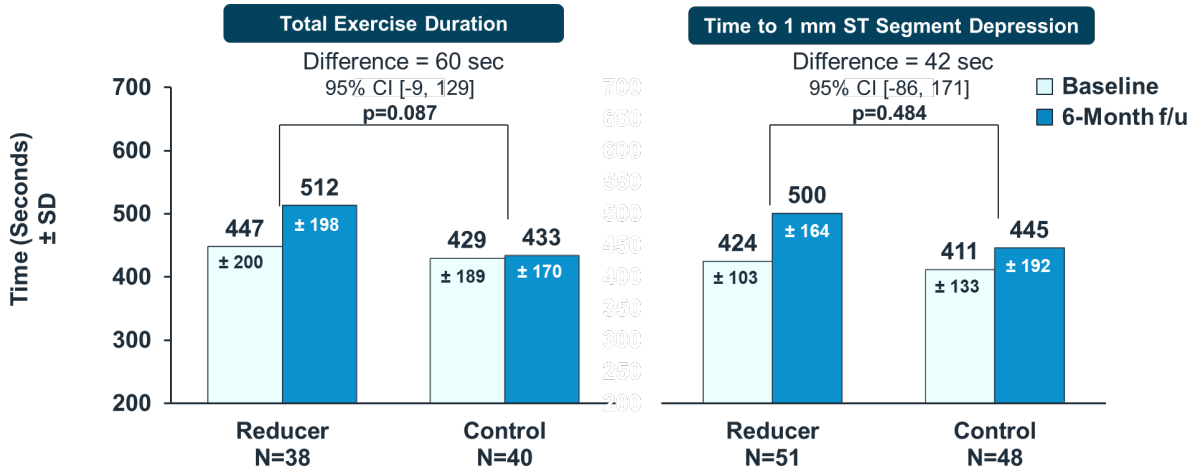
from baseline of 65 seconds of total duration of exercise on the ETT, compared to the Control group with a difference of only 4 seconds (Figure 4). The differences in time to 1 mm ST segment depression or maximal ST segment depression on the ETT were not statistically significant.

Figure 3: COSIRA: Change from Baseline on Seattle Angina Questionnaire (Paired Data)



Note: Secondary endpoint analyses were not pre-specified and did not account for multiplicity.

Figure 4: COSIRA: Exercise Tolerance Test Exercise Duration and Time to 1 mm ST Segment Depression (Paired Data)



Note: Secondary endpoint analyses were not pre-specified and did not account for multiplicity.

The findings in COSIRA are supported by the ongoing, long-term, postmarket study, REDUCER-I. Data have been collected through 5 years post-implant, with planned enrollment of up to 400 patients from up to 40 study sites in Europe. As of the most recent interim report cutoff date, 241 patients have been enrolled in the 3 arms:

- Arm 1 (n=191): de novo patients with refractory angina who have demonstrated objective evidence of reversible myocardial ischemia and have limited or no options for revascularization assessed for Reducer implantation
- Arm 2 (n=11): patients who were implanted with the Reducer in COSIRA
- Arm 3 (n=39): patients who were implanted with the Reducer under CE Mark prior to the start of the study

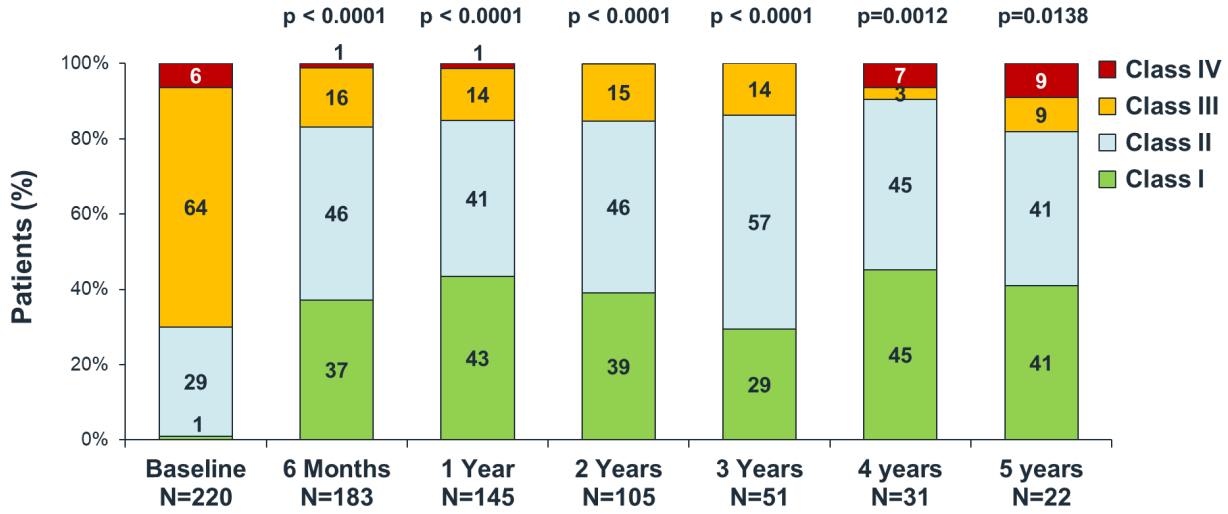
A total of 158 patients completed the 1-Year Visit, 111 completed the 2-Year Visit, 58 completed the 3-Year Visit, 32 completed the 4-Year Visit, and 23 completed the 5-Year Visit.

The primary effectiveness endpoint in REDUCER-I is the percentage of patients who experience improvement in their angina symptoms, defined as a reduction in CCS class. There were no pre-specified hypothesis tests; p-values presented are not adjusted for multiple comparisons. Data out to 5 years show an improvement in CCS class in patients with the Reducer. CCS class decreased from a mean of 2.8 ± 0.6 at baseline to 1.8 ± 0.7 at 2 years (n=105, $p < 0.0001$) and 1.9 ± 0.9 at 5 years (n=22, p=0.0138).

Improvement of ≥ 2 CCS class was seen in 30.6% of patients at 2 years (n=98) and 35.0% of patients at 5 years (n=20), and improvement of ≥ 1 CCS class improvement in 81.6% at 2 years and 80.0% at 5 years. Additionally, the percentage of patients with severe disabling angina at rest and in minimal effort (CCS class III–IV) decreased from 70.0% at baseline to 15.2% at 2 years and 18.2% at 5 years.

At baseline, 64% of patients had CCS class III and 6% had class IV angina, with 29% class II and 1% class I. By 12 months, 43% had class I angina, 41% had class II, and only 14% had class III and 1% class IV (Figure 5). These improvements were maintained through 5 years, where only 9% had class III and 9% had class IV.

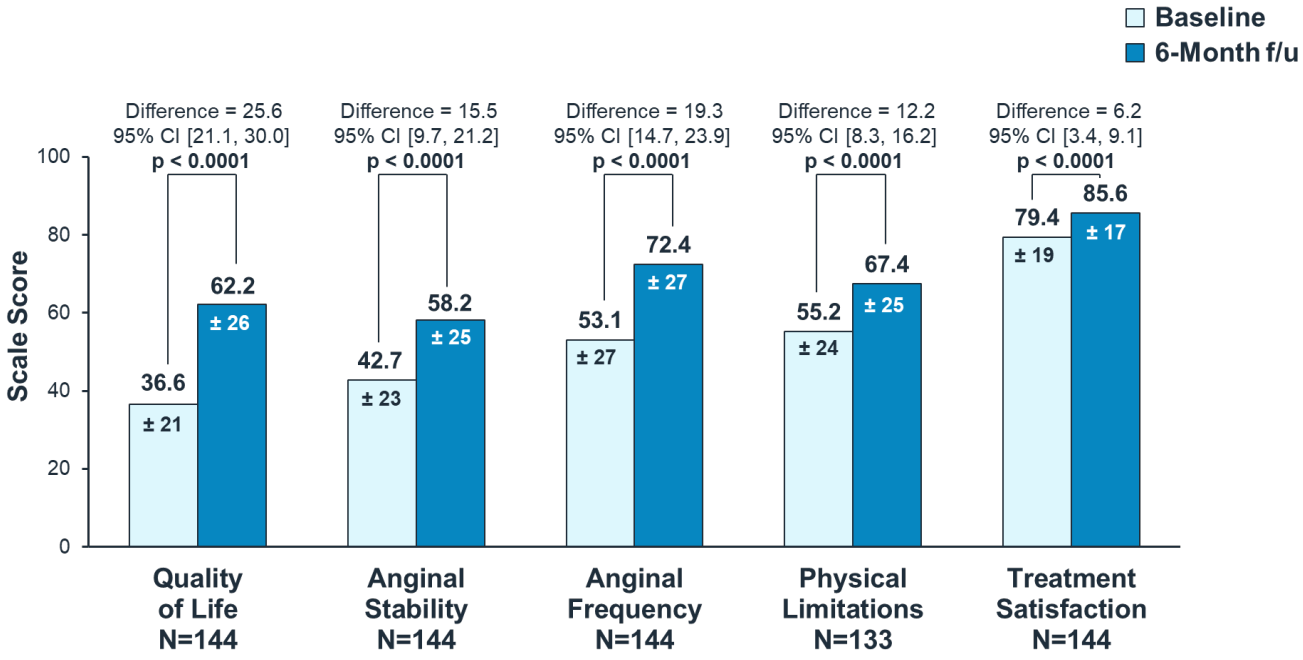
Figure 5: REDUCER-I CCS Class Distribution over 5 Years



Note: p-value is calculated using paired data and represents change from baseline to each timepoint; p-values were not pre-specified and have not been adjusted for multiple comparisons.

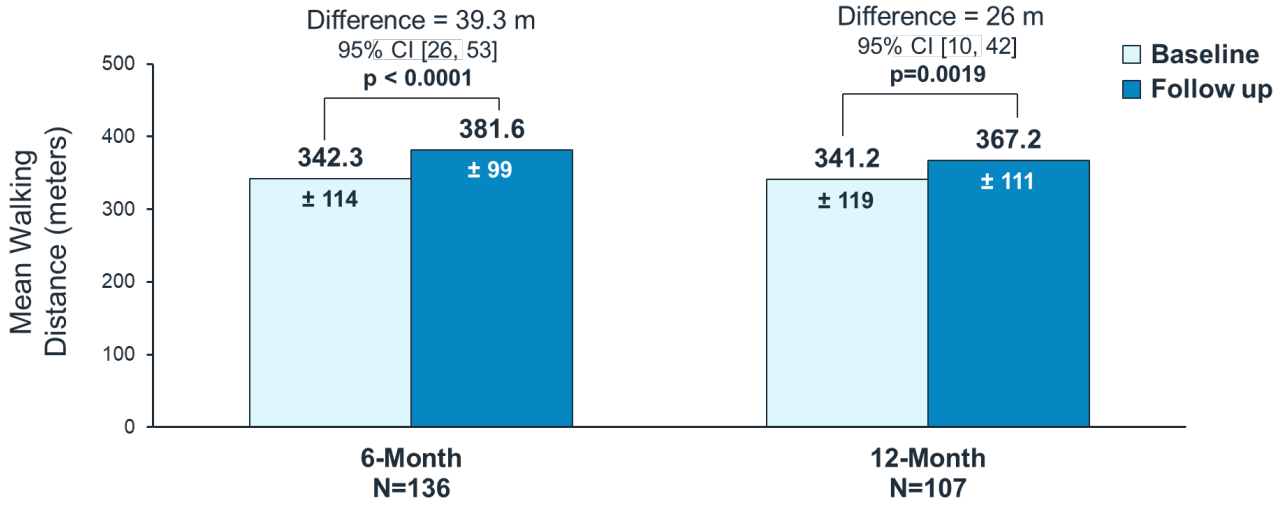
Secondary endpoints in REDUCER-I include the SAQ, six-minute walk test (6MWT), ETT, and number of emergency department visits. Patients showed an improvement of all SAQ domains at 6 months (Figure 6). Compared to baseline, distance traveled on the 6MWT (Figure 7) and exercise duration (Figure 8) on the ETT were greater at 6 months. The number of visits to the emergency department due to angina decreased from 78 visits the prior year to 22 visits in the year following implantation with the Reducer.

Figure 6: REDUCER-I: Seattle Angina Questionnaire Scores at Baseline and 6 Months (Arm 1, Paired Data)



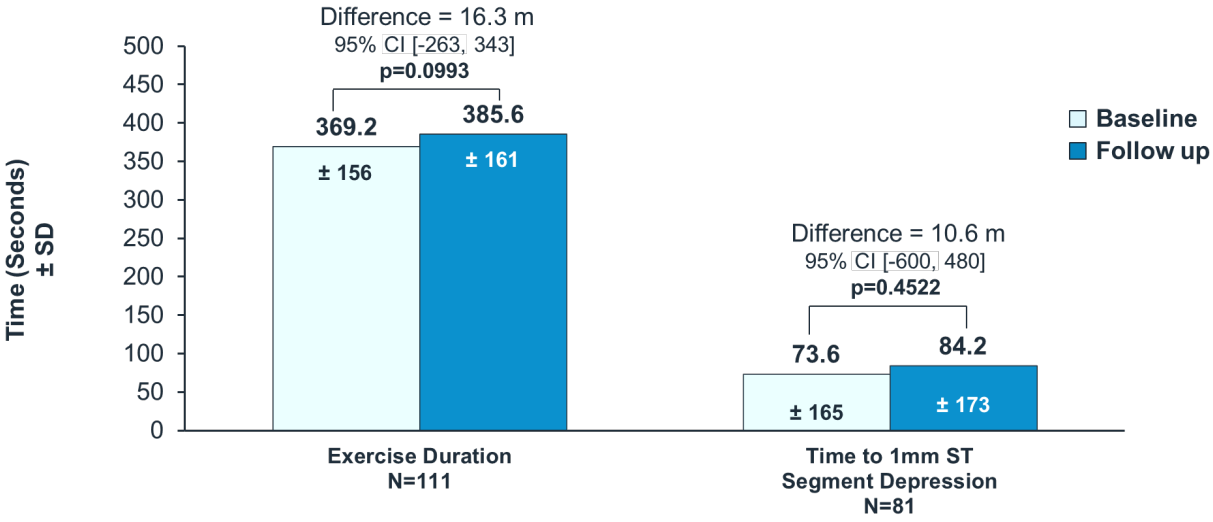
Note: p-values were not pre-specified and have not been adjusted for multiple comparisons.

Figure 7: REDUCER-I: Mean Six-Minute Walk Test Distance from Baseline to 6 Months and 1 Year (Arm 1, Paired Data)



Note: p-values were not pre-specified and have not been adjusted for multiple comparisons.

Figure 8: REDUCER-I: Exercise Tolerance Test Exercise Duration and Time to 1 mm ST Segment Depression at Baseline and 6 Months (Arm 1, Paired Data)



Note: p-values were not pre-specified and have not been adjusted for multiple comparisons.

Finally, published literature from multiple centers in Europe and Israel supports the effectiveness of the Reducer in patients with refractory angina. These investigator-initiated studies show a similar percentage of patients achieving ≥ 2 and ≥ 1 CCS class improvement as in COSIRA. More details are provided in Section 5.2.2.

Overall, the Reducer demonstrated consistent effectiveness in improving life-altering symptoms of patients in clinical trials – including a double-blind, randomized, sham-controlled clinical trial, and additional data from a supportive study – and substantial, consistent clinical evidence from numerous peer-reviewed publications.

1.7 Safety Findings

The favorable safety profile of the Reducer has been established across clinical trials including a double-blind, randomized, sham-controlled study, published literature, and postmarket surveillance. These findings demonstrate that patients treated with Reducer are not at an increased risk of serious adverse events (SAEs), major adverse events (MAEs), or death.

The safety population in COSIRA included all randomized patients and was evaluated according to the actual treatment received. Two patients who were randomized to the Reducer arm but did not receive the device were analyzed as control patients for safety. Most patients experienced at least 1 AE, with similar rates in the Reducer (64.0%) and Control (68.5%) arms. Over 90% of the AEs were mild to moderate in severity and were deemed by the CEC to be unrelated to the device or implantation procedure (Table 2).

Table 2: Relationship of Adverse Events to the Index Procedure or Device in COSIRA

By number of events (%)	Reducer	Control
Total number of events	76	93
Relationship to procedure		
Not related	68 (89.5)	88 (94.6)
Unlikely	3 (3.9)	3 (3.2)
Probably related	2 (2.6)	0
Related	3 (3.9)	2 (2.2)
Relationship to device		
Not related	69 (90.8)	92 (98.9)
Unlikely	4 (5.3)	1 (1.1)
Probably related	1 (1.3)	0
Related	2 (2.6)	0

More patients in the Control arm (20.4%) experienced SAEs than in the Reducer arm (12.0%) (Table 3). The most commonly reported SAEs were unstable angina, angina pectoris, and chest pain. No SAEs occurred prior to discharge from the hospital, and 10 occurred between discharge and the 3-month follow-up (4 in the Reducer arm and 6 in the Control arm). There was one death, which was in the Control arm and is detailed in Section 6.5.

Table 3: Serious Adverse Events by Preferred Term in COSIRA (Safety Population)

MedDRA System Organ Class Preferred Term By Number of Patients with Event (%)	Reducer		Control	
	Patients N=50	Number of Events	Patients N=54	Number of Events
Any SAE	6 (12.0)	10	11 (20.4)	24
Angina unstable	1 (2.0)	1	4 (7.4)	0
Angina pectoris	1 (2.0)	1	3 (5.6)	5
Chest pain	1 (2.0)	1	3 (5.6)	6
COPD	1 (2.0)	1	1 (1.9)	4
Myocardial infarction	1 (2.0)	1	1 (1.9)	0
Acute myocardial infarction	1 (2.0)	1	0	1
Cardiac failure chronic	1 (2.0)	1	0	0
Crohn's disease	1 (2.0)	1	0	0
Gastrointestinal hemorrhage	1 (2.0)	1	0	0
Laceration	1 (2.0)	1	0	1
Acute coronary syndrome	0	0	2 (3.7)	2
Abdominal pain upper	0	0	1 (1.9)	1
Arrhythmia	0	0	1 (1.9)	1
Cough	0	0	1 (1.9)	1
Multi-organ failure	0	0	1 (1.9)	1
Pulmonary edema	0	0	1 (1.9)	1

Note: Patients could have more than one event.

MAEs were defined as a composite of cardiac death, major stroke, and MI through hospital discharge and at 30-day, 3-month, and 6-month post-procedural evaluations. A total of 5 MAEs were reported, as adjudicated by the CEC: 1 MI in the Reducer arm, and 3 MIs and 1 cardiac death in the Control arm. More details on these events are provided in Section 6.4.

Long-term safety data from REDUCER-I support the findings from COSIRA. There were no unanticipated adverse device effects (UADEs), and no deaths were adjudicated as procedure- or device-related. Of 32 major adverse cardiac events (MACE) in REDUCER-I (Table 28), only 1 MI reported 19 days post-implant was adjudicated as unknown relatedness to device or procedure, as the CEC did not have the documentation available to definitively determine the relationship.

The safety profile of the Reducer is further supported by 12-year clinical and anatomical follow-up of 7 patients from the FIM Study. Clinical evaluation as well as computerized tomography (CT) angiography was performed 12 years after Reducer implantation. No thrombosis, occlusion, fractures, or migration were detected in any of the patients. Additional safety findings from published literature support the safety of the Reducer, with a low incidence of device- and procedure-related complications and the absence of UADEs.

1.8 Benefit-Risk

Significant Unmet Need for “No Option” Patients

The Reducer System is a novel breakthrough technology as it provides clinical benefit and symptomatic relief for “no option” patients suffering from disabling refractory stable angina. Currently, these “no option” patients are not successfully treated with standard of care to alleviate symptoms. There is no other device available to modify flow and pressure in the CS, to relieve myocardial ischemia and symptoms of angina. The Reducer is intended to be used in patients who are not amenable to revascularization procedures and/or are not responsive to available medical treatment. Therefore, the Reducer would be a viable treatment option for patients who remain symptomatic despite previous revascularization therapies and/or utilization of approved or cleared alternative therapies. As discussed above, current treatment options for refractory angina are exhausted with less than optimal results, indicating there is still an unmet need in this patient population suffering from disabling refractory angina, and novel therapeutic options for this group of patients would be welcomed by physicians and in the best interest of these “no option” patients.

Breakthrough Designation Allows for Earlier Access with Adequate Postmarket Controls

The FDA has recognized this unmet need by granting Reducer a Breakthrough Device Designation. According to published FDA guidance, FDA will only approve a PMA if it determines that there is reasonable assurance of safety and effectiveness (FDA 2018). However, as part of the benefit-risk determination for Breakthrough Devices subject to a PMA, FDA may accept a greater extent of uncertainty of the benefit-risk profile for these devices if appropriate under the circumstances, including that the uncertainty is sufficiently balanced by other factors, such as the probable benefits for patients to have earlier access to the device (e.g., a device that treats a life-threatening disease when no alternative treatments are available) and adequate postmarket controls to support premarket approval.

COSIRA Met Effectiveness Endpoint

The Reducer demonstrated effectiveness in improving life-altering symptoms in patients with angina, with a favorable safety profile. The primary effectiveness endpoint was met in COSIRA, with statistically significantly more patients in the Reducer arm (34.6%) than the Control arm (15.4%) achieving a ≥ 2 CCS class improvement at 6 months (p=0.024). This finding was confirmed in REDUCER-I, with benefits sustained through 5 years with a mean change in CCS class of 1.9 ± 0.9 (p=0.0138). Importantly, the majority of patients in the Reducer arm in COSIRA (71.2% vs 42.3% Control, p=0.003) and in REDUCER-I (81.6%) achieved ≥ 1 CCS class improvement.

The improvements in CCS class are not only statistically significant but, more importantly, clinically meaningful to patients. An improvement from Class IV to Class II, for example, indicates that a patient was unable to perform any activity without angina

or even had angina at rest and now only has slight limitation or angina during activity. Improvement from Class III to Class I takes a patient from marked limitation with symptoms with everyday activities to now only having angina during strenuous or prolonged physical activity.

These findings are reinforced with the number needed to treat (NNT) analysis for a 2 CCS class improvement of only 5.2, and the NNT for 1 CCS class improvement of 3.5. Thus, these are low numbers of patients needed to treat to provide effective improvement in quality of life, especially in this “no option” group of patients, given the favorable safety profile of the device. Considering the relatively favorable prognosis of patients with stable angina, it is clear that the goal of therapy should be targeted primarily towards improving quality of life and angina symptoms, rather than reduction of cardiovascular related mortality. Thus, the low NNT to improve symptoms is clinically significant as these severely disabled patients are expected to live a long time.

Acceptable Safety Profile

Safety findings from COSIRA, REDUCER-I, and long-term follow-up from the FIM Study demonstrate a favorable risk profile of the Reducer, particularly considering the minimally invasive nature of the procedure. These studies have demonstrated a very low incidence of device- and/or procedure-related complications and the absence of AEs not anticipated by the risk management process.

Overall Positive Benefit-Risk

The totality of the evidence, including the randomized, sham-controlled study (COSIRA), REDUCER-I postmarket study, and real-world evidence from multiple publications for Reducer, supports the reasonable assurance of safety and effectiveness. Importantly, as part of the Breakthrough Device Designation, FDA may accept a higher degree of uncertainty about the benefit-risk profile of the device at the time of approval by requiring collection of certain data in the postmarket setting rather than premarket. Neovasc has proposed a multi-center, randomized, double-blind, sham-controlled study of a minimum of 236 participants, including patients from the United States. Details on this postmarket study, REDUCER-II, are provided in Section 7. Overall, the Reducer provides safe and effective symptom relief and improved quality of life for patients who have failed other therapies and still suffer from the disabling condition of refractory angina.

2 BACKGROUND ON REFRACTORY ANGINA

Summary

- Stable angina pectoris is a disabling medical condition characterized by chest pain and discomfort that severely impact patients' quality of life.
- Patients with angina are treated with medications, balloon angioplasty, PCI, or CABG surgery; however, some patients are left with angina chest pain which is refractory to all available medical and interventional therapies.
- In the US, it is estimated that up to 1.8 million people have refractory angina, and a subset of 26,000 to 52,000 have Class III or IV angina resulting in severe limitation in their ability to perform activities of daily living.
- Severity of angina is commonly assessed by the CCS grading of angina pectoris, which ranges from class I (pain with strenuous exertion) to class IV (inability to perform any physical activity without pain). Improvement of 1 functional class represents a clinically meaningful improvement.
- These "no option" patients suffer from severely reduced quality of life and need a novel, safe, and effective therapy.

2.1 Overview of Refractory Angina

2.1.1 Angina Pectoris

Angina pectoris is the classical presentation of chronic obstructive CAD and is the symptom that most often drives these patients to seek medical attention (Agarwal et al 2010; Gaziano et al 2006; Gaziano 2007; Hess et al 2008; Kaul et al 2007; McNab et al 2006; Nordrehaug and Salem 2006; Roifman et al 2011). Patients with angina pectoris experience exertional chest pain, tightness, and pressure, or exertional shortness of breath caused by an inadequate blood supply to the heart muscle (i.e., coronary insufficiency). Angina can be unstable or stable. Unstable angina is acute or unexpected pain. Stable angina is predictable pain that occurs with exercise or stress, and it can be experienced at rest for patients with more severe angina.

2.1.2 Refractory Angina Pectoris

Angina pectoris, refractory to medical and interventional therapies, is a common and disabling medical condition, and a major public health problem that affects millions of patients worldwide (Benck and Henry 2019). Refractory angina is defined as 3 months or more of angina due to demonstrated coronary insufficiency that persists despite optimal medical therapy in patients who are no longer amenable to further percutaneous or surgical revascularization (Mannheimer et al 2002).

The clinical burden of refractory angina is growing due to an aging population and improved survival from CAD. According to data from the National Health and Nutrition

Examination Survey from 2013 to 2016, the overall prevalence of angina is 3.6% in US adults 20 years of age and older. However, a smaller subpopulation of between 26,000 to 52,000 patients have CCS class III or IV angina resulting in severe limitation in their ability to perform activities of daily living (Benck and Henry 2019).

The primary concern of patients with refractory angina is their quality of life, as opposed to mortality. Recent data indicate that mortality rates in refractory angina patients are approximately 4% per year (Henry et al 2014; Povsic et al 2015). Considering the relatively favorable prognosis of these patients, the goal of therapy is targeted primarily towards improving quality of life and reducing angina symptoms.

2.2 Measurement of Angina Severity

2.2.1 Canadian Cardiovascular Society Grading of Angina Pectoris

CCS grading was developed by the Canadian Cardiovascular Society with the purpose of defining a scale for the severity of exertional angina to evaluate the efficacy of medical and surgical therapy by comparing the patient's status before and after therapeutic interventions. The scale needed to be simple, reproducible by independent observers, and able to show small differences in angina status over time (responsiveness). The CCS grading system of the severity of effort angina appears to have been universally adopted, based on the numerous and increasingly more frequent reference to its original description. Of the 656 manuscripts citing this grading system, 87% were written in English, 28% in German, 27% in Russian, 22% in French, 2% each in Scandinavian and Spanish, and 1% in Japanese. The CCS grading system has been described in at least 18 textbooks covering topics of cardiology, pathophysiology, internal medicine, anesthesiology, and nursing. Despite potential imperfections, a satisfactory reproducibility of the CCS system of 73% was documented by Goldman, et al. This reproducibility was equal to that found for their scale (Specific Activity Scale) and significantly better than that of the NYHA functional classification, which was only 56% (Campeau 2002).

The 4 classes of the CCS range from class I, in which patients experience angina only during strenuous or prolonged physical activity, to class IV, in which patients are unable to perform any activity without angina or angina at rest (i.e., severe limitation) (Table 1). Each CCS class captures how refractory angina affects a patient's feeling and well-being, and an improvement of 1 functional class represents a clinically meaningful improvement. An improvement of 2 functional classes represents a clinically significant transformation, for example, from severe disability to mild physical limitation.

Class Endpoints Commonly Used in Studies

Similar to angina, heart failure studies have frequently used NYHA class as clinical evidence to support product approval. For example, the Summary of Safety and Effectiveness for Medtronic's InSync® Biventricular Pacing System shows approval with an effectiveness endpoint of cardiac resynchronization therapy (CRT) showing a

statistically significant improvement over control at 6 months when compared to baseline for NYHA, 6MWT, and QOL scores. The paired data showed a 1-class improvement in NYHA but improvement in both groups (68% in the treatment group vs. 38% in the control group); both groups showed improvement in QOL scores, but the number of patients who improved was greater in the treatment group (79.1%) than in the control group (66.9%) with overlapping confidence intervals. The 6MWT showed a slight increase for the control group, and a larger increase for the treatment group. The increase in the treatment group was statistically significantly greater than that in the control group although both groups showed improvement – 69% in the treatment group and 55.9% in the control group.

2.2.2 Seattle Angina Questionnaire

The SAQ quantifies the physical and emotional effects of CAD. The questionnaire is a 19-item self-administered tool that provides results in 5 scales that measure clinically important dimensions of CAD: physical limitation, anginal stability, anginal frequency, treatment satisfaction and disease perception/quality of life. A change in score of 10 points in any of the subscales equals or exceeds a change perceptible to patients and is considered to be clinically important (Spertus et al 1995). The physical limitation scale measures how daily activities are limited by symptoms of coronary disease. The scores are classified as minimal (score 75–100), mild (50–74), moderate 25–49), and severe (0–24) (Spertus et al 2002). On the anginal stability scale, lower scores indicate more frequent angina, and high scores less frequent angina compared with the previous month. A score of 50 indicates no change in anginal frequency at the patient's most strenuous level of activity (Spertus et al 1995). Higher scores indicate better levels of functioning.

2.3 Current Treatment Options

Current treatment options for refractory angina focus on medical therapy and secondary risk factor modification. First-line pharmacologic interventions include beta blockers, nitrates, and calcium channel antagonists. Low-dose aspirin and statins are also prescribed to prevent cardiovascular events. In the US, ranolazine is approved by FDA for the treatment of chronic angina. Nicorandil, a vasodilatory medication, is used to treat angina in the EU but is not approved for this use in the US.

Revascularization can be used in an attempt to increase blood supply to the heart and decrease the symptoms of angina. Current revascularization procedures include PCI with or without coronary stenting and CABG surgery; however, revascularization is not an effective treatment for all patients. Persistence or recurrence of angina after PCI may affect approximately 20–40% of patients during short- to medium-term follow-up. This persistence of angina appears to be true even when PCI is 'optimized' using physiology-guided approaches and drug-eluting stents. Persistent or recurrent angina post-PCI is associated with a significant economic burden. Healthcare costs may be almost 2-fold higher among patients with persistent or recurrent angina post-PCI

compared with those who become symptom-free (Crea et al 2019; Konigstein et al 2016).

Revascularization eliminates angina symptoms in only about two-thirds of patients with stable CAD, regardless of the choice of revascularization procedure (PCI or CABG). Therefore, about 30% of patients revascularized for stable CAD continue to experience anginal symptoms (Mahmood and Hoque 2017). Additionally, patients may not be suitable for revascularization due to diffuse coronary disease, poor target vessels, lack of conduits, or advanced/multiple comorbidities (Mukherjee 2013).

A considerable number of alternative therapeutic modalities for the treatment of severe chronic angina have been investigated over the years. These modalities include: transcutaneous electric nerve stimulation and spinal cord stimulation (de Jongste et al 1994; Lee et al 2012; Zipes et al 2012), left stellate ganglion blockade (Chester et al 2000), endoscopic thoracoscopic sympathectomy (Claes et al 1996), EECP (Arora et al 1999; Barsness et al 2001; Barsness 2001; Lawson et al 1992; Lawson et al 1996), and finally, myocardial laser revascularization (Frazier et al 1999; Gray et al 2003; Kim et al 1997; Lauer et al 1999; Leon et al 2005; McGillion et al 2010; Oesterle et al 1998; Oesterle et al 2000; Salem et al 2004). Despite extensive studies conducted to evaluate the efficacy of these strategies, most studies have failed to demonstrate an advantage over conservative treatment, placebo or sham procedure in randomized controlled trials, and none of these alternative therapeutic options have become a standard of care for refractory angina. Additional lifestyle modifications such as cognitive behavioral therapy, smoking cessation, and weight loss may also be effective (Knuuti et al 2020; Moore et al 2007).

Currently there is no device available to modify flow and pressure in the CS, to relieve myocardial ischemia and symptoms of angina.

2.4 Patient Medical Need

Over the last few decades, increasing numbers of coronary revascularization procedures along with improved drug and device therapies have greatly increased the life expectancy of patients with CAD. However, despite such advances in medicine, there are still a considerable number of patients who remain severely disabled by chronic refractory angina pectoris. This group of patients is rapidly growing, as available improvements in cardiovascular care have continued to extend life expectancy without the ability to treat symptoms. “No option” patients include those who have significant disability with limiting symptoms resulting from myocardial ischemia, multiple medications, and frequent hospital admissions, despite optimal medical therapy. Severe diffuse CAD leaves these patients not amenable to further revascularization by CABG surgery or by PCI. Neovasc continues to receive requests for Compassionate Use in the US and Canada for this patient population as they remain with no treatment options for their debilitating condition. Patients with refractory angina are in need of a novel, safe, and effective therapy.

3 PRODUCT DESCRIPTION

Summary

- The Reducer is an implantable device designed to improve perfusion to ischemic territories of the myocardium in patients suffering from chronic disabling angina, refractory to medical and interventional therapies.
- The Reducer device is pre-mounted on a balloon catheter and inserted percutaneously through the right or left internal jugular vein. Three radiopaque markers on the catheter help ensure correct placement.
- The narrowing in the CS is intended to establish a pressure gradient 4–6 weeks after implantation of the Reducer, after all but the central narrow part of the metal mesh is covered with tissue ingrowth.
- The CS narrowing and pressure elevation alter venous pressure. This mechanism of action is similar to that of the Beck surgical procedure used in the 1950s and 1960s.

3.1 Proposed Indication

The Reducer System is intended for patients suffering from refractory angina pectoris despite guideline directed medical therapy, who are unsuitable for revascularization by CABG or by PCI.

3.2 Reducer System Overview

The Reducer System is an implantable device designed to establish a narrowing in the CS and is intended to improve perfusion to ischemic myocardium in the presence of reversible ischemic heart disease to alleviate the symptoms of refractory angina. The Reducer is implanted percutaneously through the right or left internal jugular vein into the CS.

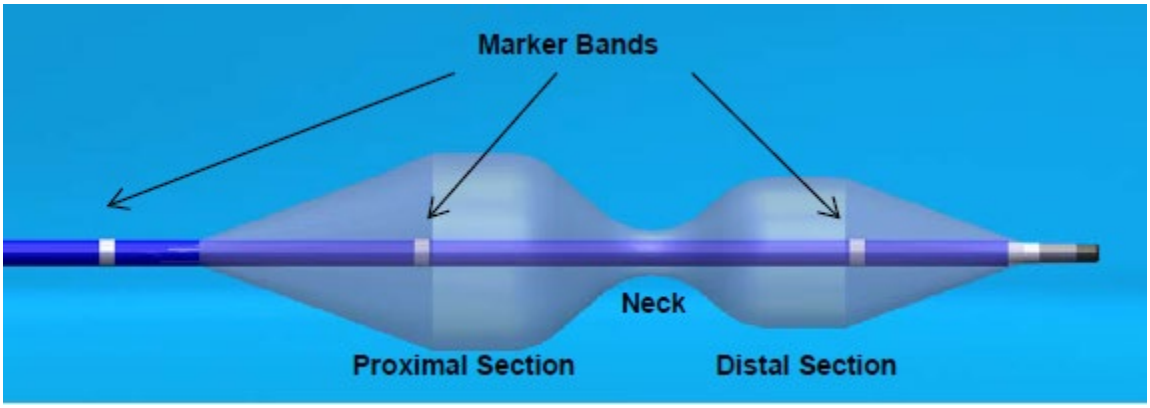
The Reducer is made of surgical grade 316L stainless steel, laser cut into a pre-specified geometric pattern with flexible longitudinal struts and no welding points. The use of stainless steel allows the device to be expanded to a final profile determined by the inflation pressure of the deployment balloon used for implantation.

The semi-compliant delivery balloon is available in one single size, and the final expanded diameters are dependent on the inflation pressure, compatible with CS diameters of 9.5–13 mm at the proximal implant site.

The proximal and distal portions of the device are configured to different diameters, based on balloon expansion, allowing the device to conform to the tapered configuration of the anatomy of the CS, with the center narrowing consistently 3 mm in diameter. It is also possible to expand the central narrowing and remove the narrowing, if so desired.

The Reducer is pre-mounted (crimped) on the Reducer Balloon Catheter, which is an over-the-wire catheter with a unique hourglass shaped balloon (Figure 9). The proximal and distal portions of the balloon have differing diameters to conform to the taper typically encountered in the CS. Two radiopaque markers on the catheter shaft mark the location of the crimped Reducer on the deployment balloon. A third marker located just proximally to the balloon is used to assist the operator to visualize when the balloon section of the catheter is completely outside of the tip of the guide catheter. The Reducer Balloon Catheter is inflated to expand the device and appose it with the vessel wall. The Reducer Balloon Catheter is then deflated and removed from the CS, leaving the device permanently implanted.

Figure 9: Neovasc Reducer Balloon Catheter



3.2.1 Device Generations

The Reducer device used in the FIM clinical study was the first generation E15 version. The Neovasc Reducer System underwent a design revision prior to being finalized in its current state in 2009. The COSIRA trial initiated in 2010 was conducted using the current generation, the B17W version. The differences between the two generations were primarily related to an improved catheter delivery system, whereas the Reducer itself remained substantially the same in both generations. The Reducer in the first generation was hand-crimped by the physician to a commercially available cylindrical shaped balloon catheter. Since the balloon on the delivery catheter was cylindrical in shape, the system relied on the stiff center or “neck” portion of the Reducer to resist expansion by the cylindrical balloon and thereby achieve the desired hourglass shape once deployed in the CS.

While the first generation system achieved the desired result in terms of final device shape and size of the prosthesis on implantation, this delivery system had several disadvantages:

Adequate supplies of the compatible balloon catheter were required to be available for use during the procedure, in the appropriate size ranges and lengths to ensure the Reducer was deployed successfully.

Hand-crimping the device to the balloon in the catheterization laboratory introduced risks that could not be easily mitigated by design or prevented by labelling. These risks included: device dislodgement, device migration, potential device and vessel damage due to protruding areas of the stent, potential for balloon damage and rupture due to manual crimping, and inconsistent device deployment and profile.

The stiff midsection of the first generation Reducer was difficult to consistently crimp by hand to achieve the desired crossing profile for the device.

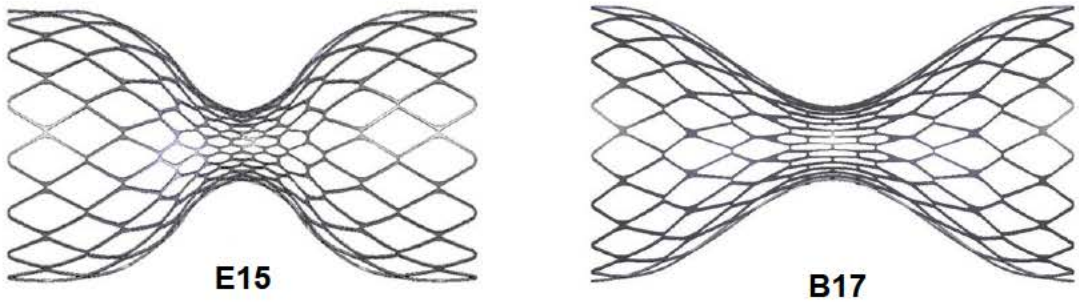
Finally, industry standards and state of the art for coronary stents is to provide these devices in a finished configuration. This minimizes time lost in device prep and reduces the technical challenge of expanding an hourglass-shaped device with a cylindrical tube-shaped balloon.

To ensure the device would consistently perform as intended, a balloon delivery catheter was designed and developed specifically for the Neovasc Reducer. With this change, some of the design requirements for the Reducer were eased. A stiff stent midsection was no longer a requirement to resist balloon expansion and achieve the desired tapered hourglass shape upon deployment; this in turn improved device stiffness and kink resistance of the mounted stent and reduced the need for a larger (11 F) guiding catheter. Finally, an important safety feature was added to the design: the ability to expand the middle of the device in the event that CS access becomes necessary. This feature was not absent in the previous design but was more technically challenging than deemed necessary if complete expansion of the device was needed.

Based on these considerations, a dedicated, custom-made delivery system for the Reducer was designed to conform to the finished, desired shape of the expanded Reducer. The Reducer was slightly modified in the midsection as the device shape was now determined by the delivery system. This modification also provided increased flexibility during delivery, and a more easily expandable midsection for CS access if necessary.

The differences between the architecture of the first and second generation devices are minimal, and, upon deployment, the devices are essentially the same with no change in the proximal and distal sections of the prosthesis. Both devices are deployed for apposition to the wall of the CS at the proximal and distal ends, with only minor differences in the narrowed-neck region. The neck stiffness was reduced by increasing the length of the axial cuts in the neck area of the device. To maintain substantially the 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 strut density (by surface area) in the neck region. 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 model B17W, as shown in Figure 10.

Figure 10: Comparison of Reducer Models E15 and B17W



The raw materials for both configurations remained the same (stainless steel 316L), as did the production process, heat treatment, electropolishing, and sterilization methods.

3.3 Mechanism of Action

3.3.1 Pathophysiology of Angina

Microvascular dysfunction with obstructive coronary disease has been described by Paolo Camici and Fillipo Crea (Camici and Crea 2007; Ido et al 2001).

> In the healthy heart, blood flow in the subendocardial myocardium is normally higher than in the subepicardial layers of the myocardium. Moreover, during exercise and increased demand, a physiologic compensatory mechanism causes selective sympathetically mediated vasoconstriction with increased resistance to flow in subepicardial vessels, favoring subendocardial perfusion and allowing an appropriate augmented contractility. The ratio of endocardial to epicardial blood flow averaged throughout the cardiac cycle is approximately 1.2:1 due to preferential dilation of the subendocardial arterioles, causing a large increase in diastolic flow in the subendocardium.
>
> In the presence of a significant epicardial coronary artery stenosis, however, this compensatory mechanism, which normally preserves preferential blood flow to the subendocardial myocardium, becomes dysfunctional and the transmural myocardial perfusion is redistributed toward the subepicardial layers of the left ventricle. The normal ratio between subendocardial and subepicardial blood flow is significantly reduced from 1.2 to 0.5, reflecting a shift of blood from the more highly resistant subendocardial blood vessels to the less resistant subepicardial blood vessels. Thus, the perfusion of the subendocardium during stress becomes compromised, causing ischemia, impaired contractility, and elevated left ventricular end diastolic pressure (LVEDP), with consequent angina symptoms and shortness of breath. Elevated LVEDP exerts an external pressure on the subendocardial capillaries and arterioles, which further increases the resistance to flow, contributing to the vicious cycle of subendocardial ischemia (Vermeltfoort et al 2011).

Akira Ido (Camici and Crea 2007; Ido et al 2001) and colleagues demonstrated this concept in a canine model. The increase in intra-myocardial pressure during severe ischemia and the redistribution of blood from the subendocardium to the subepicardium was described as follows:

> Elevating backward pressure in the coronary venous system results in a slight dilatation of the diameter of arterioles that leads to a significant reduction to vascular resistance in the subendocardium. Consequently, blood flow in the ischemic subendocardial layers of the myocardium is enhanced, contractility improves, and LVEDP decreases.

Thus, the result of the decreased subendocardial vascular resistance is redistribution of blood from the less ischemic subepicardium to the more ischemic subendocardium with normalization of the endocardial to epicardial blood flow ratio, which leads to symptom relief (Camici and Crea 2007; De Maria et al 2018; Ido et al 2001; Mohl et al 1984; Syeda et al 2004).

3.3.2 Preclinical Studies of CS Pressure Elevation

The benefit of CS pressure elevation on myocardial preservation and ischemia relief has been demonstrated in numerous independent preclinical experiments. The following 3 landmark preclinical experiments represent the proof of concept and elaborate on the mechanism of action of CS pressure elevation as an effective antimyocardial ischemia therapy (Guerci et al 1987; Ido et al 2001; Sato et al 1996).

As stated in Section 1.5, preclinical experiments preceded and set the basis for the clinical evaluation. Neovasc conducted preclinical animal studies on the Reducer System in the miniature swine model. The suite of studies performed by Neovasc included 2 pilot animal studies and one pivotal animal study spanning a preclinical research period of 7 years from 2002–2009 and included 52 animals. The individual study endpoints ranged from acute to 6 months. 39 of the 52 animals were from two non-GLP feasibility studies from which FDA was provided with final non-GLP study reports and a final pathology reports. The last 13 swine subjects were subjects in a pivotal non-GLP study from which FDA was provided a final study report, source records containing data and information from implants and Reducer delivery system performance, and a final pathology report containing macroscopic and microscopic data from the chronic animal subset of 7 animals.

The evaluators of these studies included an internationally-recognized cardiologist, 2 highly experienced interventionalists, and 3 board-certified pathologists (1 human and 2 veterinary) who independently reported similar findings. Although not strictly GLP, the studies were undertaken using protocols and standard operating procedures that included modern methods of humane animal experimentation in experienced and respected international animal facilities by trained support personnel, consistent with the level of preclinical research typically conducted for first in man or breakthrough

technology. Importantly, the gross and histologic assessments were provided by independent examiners at US GLP pathology laboratories. The methods included sophisticated pre-operative preparation, interventional procedures and monitoring, imaging, echocardiographic and angiographic assessment, performance and handling assessment, and gross and histological processing.

Final non-GLP study reports and final pathology reports have been provided to FDA to support both the IDE and the PMA submissions. Additionally, source data (animal records) were provided for 13 animals from the pivotal study (b) (4) . Information in Table 4 summarizes the information provided to FDA for each study.

Table 4: Summary of Reducer System Animal Studies

Type of Animals and N	Endpoints	Data and Information Submitted to FDA
Pilot Study (b) (4) , 2002–2005, First Generation Device (E15)		
34 miniature swine (8 ischemic models divided to 4 each in Reducer implant vs. no implant cohorts; 26 non-ischemic recipients who received Reducer) - Safety Arm: o acute: n=7 o 3 m: n=5 o 6 m: n=6 o 2–4 m: n=8 - Effectiveness: o Ischemic arm: ▪ 6 m: n=4 o Control ischemic no implant: ▪ 6 m: n=4* * 3 did not survive to endpoint	Acute and Chronic survival, patency, acceptable systolic, diastolic and mean aortic pressures, acceptable or improved ventricular contractility and myocardial perfusion, acceptable endothelialization of Reducer implant at chronic time point, absence of thrombosis, embolization, migration, perforation.	Final non-GLP Study Report Final Pathology report
Pilot Study (b) , May 2006, First Generation Device (E15)		
5 miniature swine - Acute: n=1 - Chronic: o 2.5 m: n=1 o 3.5 m: n=1 o 6.5 m: n=1 1 animal not studied and expired after coronary sinus found too small to implant	Gross and histological outcomes reported non-GLP.	Final non-GLP Study Report Final Pathology report

Type of Animals and N	Endpoints	Data and Information Submitted to FDA
Pivotal Study (b) (4) , January–April 2009, Current Generation Device (B17W)		
13 (2 domestic, 11 miniature) - Acute: n=4 - 24 h: n=2 - Chronic: o 57 d: n=2 o 104 d: n=3 o 140 d: n=2	Acceptable performance and handling, freedom from migration, perforation, thrombosis, acceptable endothelialization, low level inflammation and injury.	Final non-GLP Study Report and Animal Records (source data) which demonstrated: 100% successful implants in size-appropriate coronary sinus recipients. Acceptable regional tissue-contacting gross pathology and histology with absence of migration, perforation. Final Pathology Report which demonstrated: 100% CS lumen endothelialization, endothelialization and tissue proliferation at proximal and distal ends of Reducer with 60% or less coverage of mid-section struts and preservation of lumen from proximal to distal through midsection.

This collection of studies included both pilot and pivotal work in ischemic and non-ischemic models culminating in a 13-pig pivotal study that included 4 acute, 2 subacute, and 7 chronic animals signed by an experienced Regulatory Affairs professional. The 7 chronic animals were included in a 2009 pathology report for Reducer implants signed by Dr. Serge Rousselle, a recognized expert in pathological assessment of medical devices at a well-known US histopathology laboratory. The Reducers were sectioned at 3 levels (proximal, mid, and distal) and evaluated by light microscopy and histomorphometry. The final pathology report concluded there was complete endothelialization of the luminal surface of the coronary sinus as early as 2 months, and very low levels of inflammation at all time points and in all sections.

Tissue Proliferation and Coverage of the Reducer

Implantation of the Reducer is performed with an intentional approximately 10% oversizing of both wide ends of the device. Oversizing is important and helps to achieve 2 goals: (1) to anchor into the elastic vessel wall to help prevent migration, and (2) to trigger a process of injury-induced tissue proliferation, which at 57 days of implantation, as demonstrated in the pivotal non-GLP animal study, covers the gaps between the metal struts and aligns with preclinical feasibility studies demonstrating 15-minute and 6-month post-implant outcomes that establish the pressure gradient across the narrow

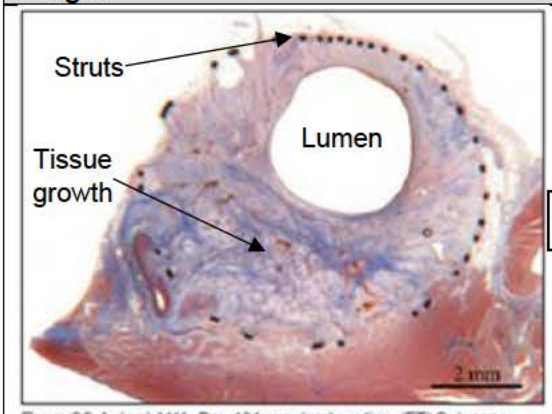
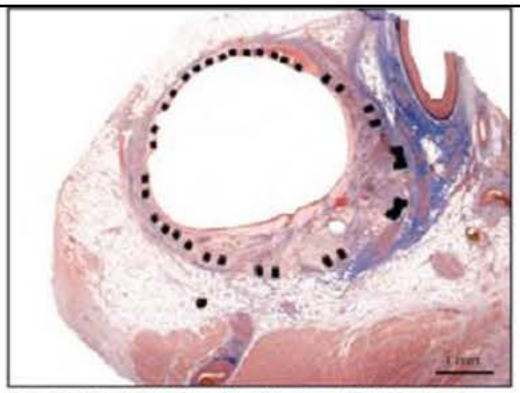
center of the device. The pressure gradients were reported to FDA in a final study report that was non-GLP feasibility data (b) (4)

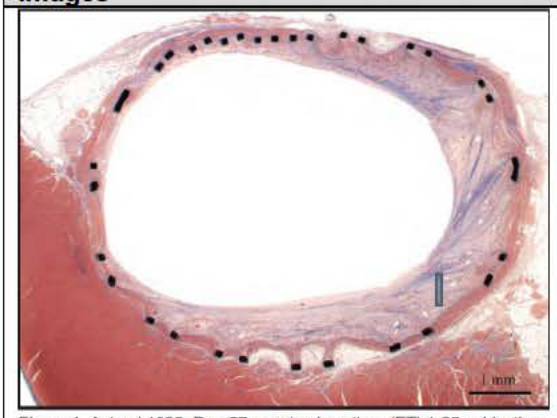
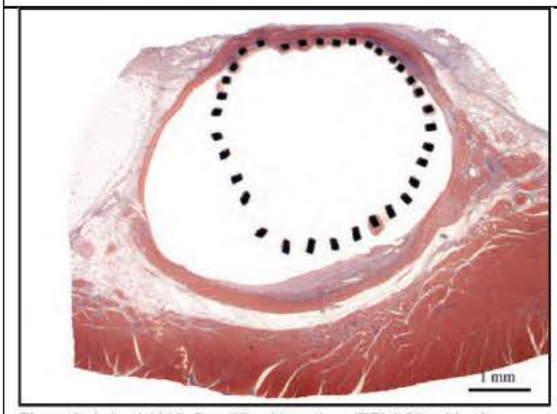
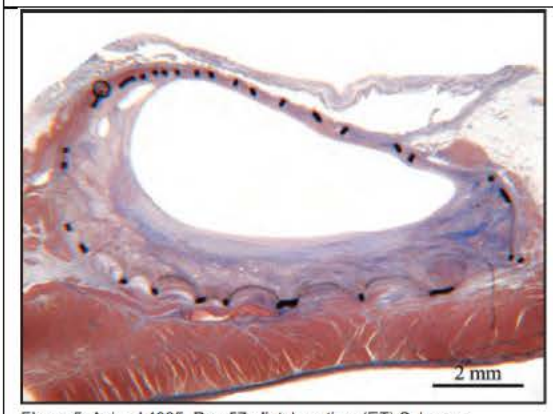
Importantly, since the narrow central part of the device is not in direct contact with the vessel wall, and does not cause any vessel wall injury, there is no trigger for tissue growth at this point, and therefore, the vessel lumen at the center of the device remains patent. If a central narrowing is observed in the immediate post-implantation angiography, it is believed to be the result of spasm of the thin wall of the CS onto the metal mesh.

Both wide ends of the Reducer interact with the vessel wall and stimulate tissue proliferation to cover the metal struts and the gaps between the struts. As demonstrated in pre-clinical studies, in all cases the tissue growth covers the wide ends of the Reducer. In some cases, but not all, the tissue proliferation also covers the metal struts at the narrow center of the Reducer. The proliferative process is less intense and sometimes absent in the center of the Reducer, as there is no direct interaction between the struts and the vessel wall at this point. Neointimal coverage of the center struts in the mid-section is a result of neointimal encroachment from either end, proximal or distal, over time and therefore has variability. Embedding both wide ends of the Reducer in tissue is sufficient to create a tube-shaped narrowing even when the center struts are not fully endothelialized.

The Executive Summary of the pivotal study pathology report concluded that the deployment of the Reducer stent in healthy mini-pigs for 57, 104 or 140 (±1) days was associated with optimal local tissue toleration (no to very low foreign body response) and favorable healing characteristics (fully endothelialized, mature and stable neointima with no residual fibrin). The deployment characteristics of the Reducer resulted in overdistention of the proximal and distal ends and deep embedding of the stent struts within the sinus wall. There was compensatory neointima proliferation that restored the wall integrity and maintained lumen patency. Conversely the mid-stent level showed undersizing of the stent and malapposition where the stent was free in the vascular lumen or partially attached to the wall by mature neointima. Stent malapposition did not produce any microscopically appreciable adverse changes (no progressive thrombus, no stenosis, no occlusion or erosion of the endothelium). Figure 11 shows both spectrums of mid-section coronary sinus coverage.

Figure 11: Representative Histology Slides from Pivotal Study Pathology Report

Images	Notes
 Figure 25. Animal 1111, Day 104, proximal section, (ET) Subgross. Proximal	
 Figure 27. Animal 1111, Day 104, mid section, (ET) 1.25x objective magnification. Mid	This series of images shows wide ends and narrow center of the Reducer are covered with tissue overgrowth. Lumen of the CS is narrowed, and stent struts are covered with a thin neointima in approximately half of the circumference and thicker neointima and endothelium in the remaining half. Reducer is not occluded by tissue overgrowth. CS narrowing is established.
 Figure 29. Animal 1111, Day 104, distal section, (ET) Subgross. Distal	

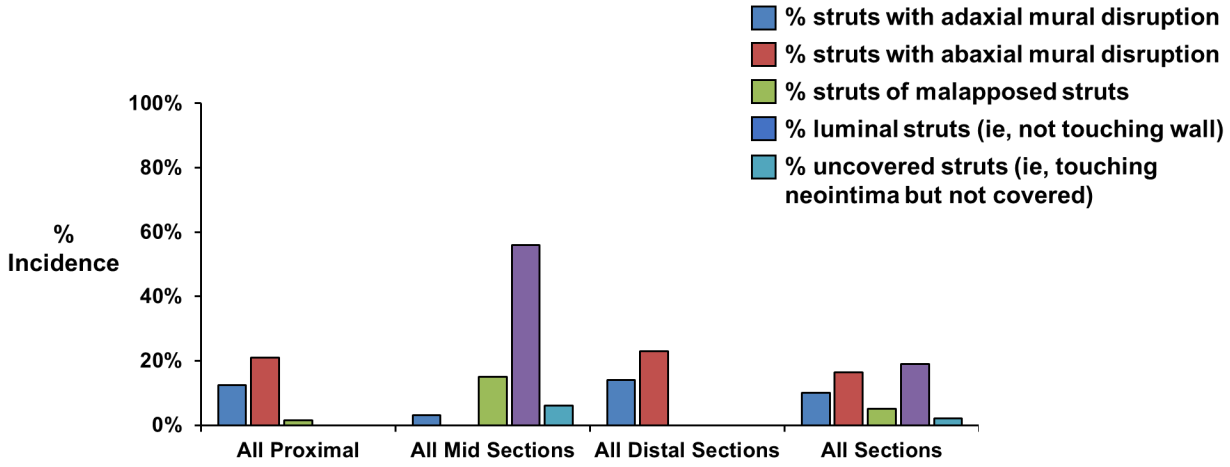
Images	Notes
 Figure 1. Animal 1035, Day 57, proximal section, (ET) 1.25x objective magnification. Proximal	
 Figure 3. Animal 1035, Day 57, mid section, (ET) 1.25x objective magnification. Mid	This series of images shows wide ends of the Reducer are covered with tissue overgrowth. Narrow center is not fully covered by neointima; only the position from 10 o'clock to 2 o'clock is covered. CS narrowing is established; absent thrombosis, granulomas, or other adverse tissue findings.
 Figure 5. Animal 1035, Day 57, distal section, (ET) Subgross. Distal	

The totality of the histopathology data demonstrates evidence that cellular coverage is consistent with Neovasc's physiologic findings in non-GLP efficacy and safety studies. The pathology report stated that mid-planes of the Reducer section often showed a narrower stent profile with many struts free in the lumen consistent with Reducer

design. The number of free struts was counted to assess the degree of stent-coronary sinus size reduction; the image below is excerpted from the board-certified pathologist's report (Figure 12).

Figure 12: Evidence of Endothelial Strut Coverage from Pathology Report

(b) (4)



Importantly, the mid-section strut coverage for the struts touching neointima of the lumen of the CS (light blue bars in Figure 12) was predominantly complete with < 10% uncovered struts. Mid-section strut coverage for those struts not touching the CS wall (purple bars in Figure 12) was less than 60%. It should be noted that mid-section strut coverage is not necessary to achieve physiologic effect, which was demonstrated in the early feasibility study (b) (4) where mean post-implantation pressure gradients were reported at 15 minutes (3.71 ± 1.75 mmHg) and 2–6 months (2.83 ± 1.47 mmHg), with the initial pressure gradients likely due to due to coronary sinus spasm that disappeared following nitroglycerine and the later gradients attributable to tissue growth. Furthermore, the non-injurious nature of tissue growth in the center of the Reducer is lumen-sparing, creating free unidirectional flow.

The Reducer System was tested in the porcine model in order to demonstrate safety and performance of the device in a dynamic physiological environment. Testing was conducted on both the original (E15) and current (B17W) Reducer model designs. The results show that the device is reliably and easily implanted and that when properly sized and in animals absent of extreme tortuosity in the CS, the animals provided a reasonable simulation of the human experience and outcome. The animals survived until their chronic study date, and the gross and microscopic findings were acceptable given the limitations of the animal model and well within the expectations for a biologically variable system. These outcomes and documentation provide reasonable evidence of safety in animals, and this information is now reinforced with a substantial body of clinical data. Additionally, the pathology report demonstrates a proof of concept for the mechanism of action.

This collection of studies included both pilot and pivotal work in ischemic and non-ischemic animal models. These experiments evaluated the safety, feasibility, and efficacy of Reducer implantation in a swine model with and without myocardial ischemia. In performance evaluations provided to FDA, among the 13 pigs in the pivotal non-GLP study, there were no instances of vessel tear or occlusion following the procedures in appropriately sized vessels as verified by angiography and histopathology. One coronary sinus tear occurred in an animal that was implanted contrary to the IFU in an overly small CS and caused a dissection, tamponade, and death.

Overall, the preclinical studies demonstrate acceptable *in vivo* performance for: introduction of the Reducer; location of the device at the target anatomy (including some extension into the azygous which is contiguous with the CS in swine); deployment of the device; angiographic visualization of the device, delivery system and all required steps in the procedure; and re-evaluation of the device at the appropriate follow-up procedures.

3.3.3 Surgical Augmentation of CS Pressure

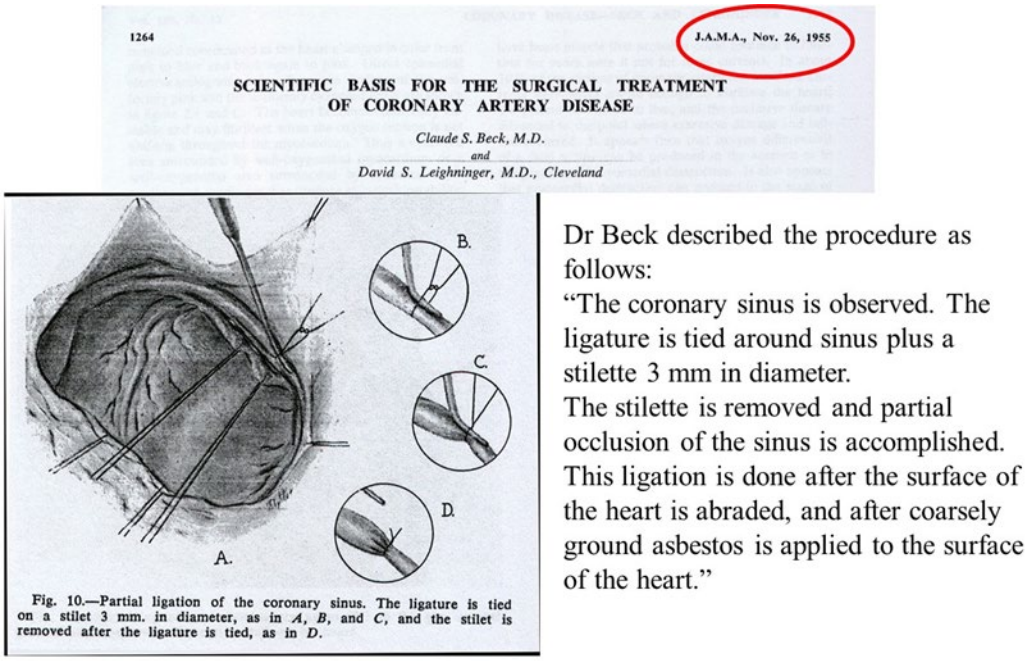
Augmentation of CS pressure for the treatment of chronic angina is a long-standing concept. In the 1950s and 1960s, Claude Beck performed a surgical narrowing of the CS to achieve redistribution of myocardial blood flow into ischemic territories of the myocardium with remarkable success (Beck and Leighninger 1955; Sandler et al 1967). Beck created a 60–70% narrowing of the CS to achieve a 3 mm residual lumen diameter in patients with severe disabling angina (Figure 13). The therapeutic results included significant relief of angina symptoms, improved functional class, and a reduced 5-year mortality rate (Mannheimer et al 2002; Mukherjee et al 2001; Rouleau and White 1985; Sato et al 1996).

Beck's preclinical and clinical work demonstrated that the success of the Beck Procedure was likely driven by elevated CS pressure, which triggered protective mechanisms that improved perfusion of ischemic myocardium. Beck's studies have been duplicated by a number of other surgeons with equally positive results – the procedure led to considerable relief of angina symptoms, allowing the patients to return to work and activities and possibly increasing life expectancy.

A comparative study of 45 patients was conducted in Uppsala with a mortality of 13% (6/45). At the time of surgery, 80% of patients were totally incapacitated, presumably in poorer condition than those reported by Brofman from Beck's clinic. Thirty-two patients (75%) reported freedom or great relief from symptoms. At the time of the operation, only 9 patients (20%) were fit for work; at follow-up 23 patients were employed full-time and 3 were part-time (58%) (Wising 1963). The Beck Procedure was so successful that it became a standard of care for treating patients with angina pectoris in the 1950s and 1960s before CABG became mainstream. The open-chest Beck Procedure is, however, considered too high-risk in patients for whom further revascularization is not an option,

and thus is not suitable for the group of “no option” patients who continue to suffer from chronic refractory angina pectoris despite optimal medical treatment (Beck et al 1951; Sandler et al 1967; Wising 1963; Zoll et al 1951).

Figure 13: Excerpted Image from Beck 1955



1264 J.A.M.A., Nov. 26, 1955

SCIENTIFIC BASIS FOR THE SURGICAL TREATMENT OF CORONARY ARTERY DISEASE

Claude S. Beck, M.D.
and
David S. Leighninger, M.D., Cleveland

Fig. 10.—Partial ligation of the coronary sinus. The ligature is tied on a stilet 3 mm. in diameter, as in *A*, *B*, and *C*, and the stilet is removed after the ligature is tied, as in *D*.

Dr Beck described the procedure as follows:
“The coronary sinus is observed. The ligature is tied around sinus plus a stilette 3 mm in diameter.
The stilette is removed and partial occlusion of the sinus is accomplished. This ligation is done after the surface of the heart is abraded, and after coarsely ground asbestos is applied to the surface of the heart.”

Western Reserve University School of Medicine and the University Hospitals

JAMA 1955,159 (13):1264-1271

Later, Mohl and colleagues used a closed loop CS balloon system to automatically occlude and release the CS to elevate CS pressure (Mohl 1984; Mohl et al 1984). Recently, CS pressure elevation using the pressure-controlled intermittent CS occlusion system (PICSO) was shown to improve index of microcirculatory resistance and reduce infarct size in patients with anterior ST-elevation MI (De Maria et al 2018).

3.3.4 CS Reducer Mechanism of Action

The Reducer is a stainless-steel mesh designed to create a focal narrowing in the lumen of the CS to generate a pressure gradient across the CS. As mentioned above, the Reducer device is pre-mounted on a customized hourglass shaped balloon catheter. When inflated, the expanded balloon gives the metal mesh its final hourglass configuration. The narrowing within the CS and the pressure gradient across the device are established 4–6 weeks after implantation, after all but the central narrow part of the metal mesh should be covered by tissue ingrowth.

In the presence of myocardial ischemia, the device is intended to improve perfusion to ischemic territories of the myocardium by forcing redistribution of blood from the less ischemic subepicardium to the more ischemic subendocardium, thus alleviating the symptoms of angina. The Reducer is implanted percutaneously via the right or left

jugular vein into the CS. The semi-compliant delivery balloon is available in one single size, and the final expanded diameters are dependent on the inflation pressure. The Reducer is designed to fit the range of anatomies encountered in most patients, and it is compatible with CS diameters of 9.5–13 mm at the proximal implant site. The proximal and distal portions of the device are configured to different diameters, based on balloon expansion, allowing the device to conform to the tapered configuration of the anatomy of the CS, with the center narrowing consistently 3 mm in diameter.

Implantation is performed with an intentional 10–20% oversizing of both wide ends of the device. Oversizing is important and helps to achieve two goals: (1) to anchor into the elastic vessel wall to help prevent migration and (2) to trigger a process of injury-induced tissue proliferation, which within 4–6 weeks after implantation should cover the gaps between the metal struts to establish the pressure gradient across the narrow center of the device. Importantly, since the narrow central part of the device is not in direct contact with the vessel wall, and does not cause any vessel wall injury, there is no trigger for tissue growth at this point, and therefore, the vessel lumen at the center of the device remains patent. If a central narrowing is observed in the immediate post-implantation angiography, it is likely the result of spasm of the CS's thin wall onto the metal mesh. As the Reducer is a stainless steel mesh, the central narrowing is intended to be easily dilated if needed, using a 5–8 mm balloon, at any time after implantation.

This presumed mechanism of action is further supported by scientific reports showing reduction of myocardial ischemic burden, improvement in diastolic function, and improvement in systolic left ventricular function, which may suggest a potential clinical benefit not only in patients with angina in the presence of obstructive CAD, but also in patients with angina due to microvascular disease, cardiomyopathies, and/or diastolic dysfunction (De Maria et al 2018; Giannini et al 2017; Palmisano et al 2020; Szekely et al 2019).

4 REGULATORY AND DEVELOPMENT HISTORY

Summary

- The Reducer System is marketed in 18 countries outside of the US, and more than 2,500 units have been distributed.
- In the US, Breakthrough Designation was granted in 2018 based on the potential for the Reducer to provide clinical benefit and symptomatic relief to "no option" patients suffering from chronic refractory angina, a population with a significant unmet need.
- The Reducer clinical development program includes an FIM Study, FIM 3 Year Follow-up, FIM 12 Year Follow-up, a 3-arm postmarket observational study which includes 11 patients from the treatment arm in COSIRA to obtain long-term data, and a multi-center, prospective, randomized, double-blind, sham-controlled clinical trial.

4.1 Regulatory History

The Sponsor submitted an Investigational Device Exemption (IDE) in May 2010, and at the same time submitted the COSIRA study in the EU and Canada where approval was obtained in June 2010 to initiate the study. Neovasc chose to pursue the study in the regulatory jurisdiction where it was approved.

The Reducer System received CE Mark in 2011, while the COSIRA study was being conducted. Despite receiving the CE Mark, the Sponsor chose not to launch the product until the COSIRA study was completed and a final analysis was conducted. The COSIRA final report was completed in November 2014. The Sponsor began a very limited launch of Reducer in 2015 in 8 countries. The Sponsor continued the controlled launch of the Reducer due to limited resources and the challenges of obtaining reimbursement coverage for any new device.

The Reducer System is currently distributed in 18 countries: Austria, Belgium, Cyprus, Denmark, Finland, Germany, Israel, Italy, Norway, Poland, Portugal, Saudi Arabia, Slovenia, Spain, Sweden, Switzerland, the Netherlands, and the United Kingdom. As of August 2020, more than 2,500 units have been distributed since 2015 outside the US. The device has not been withdrawn from the market in any country for any reason(s) related to the safety or effectiveness of the device.

The Sponsor submitted an IDE in September 2016, with approval obtained in November 2017. While the IDE was under review, in October 2017, FDA published the draft Breakthrough Devices Program guidance which is intended to help patients have more timely access to medical devices by expediting development, assessment, and review, while preserving the statutory standards for premarket approval, consistent with the Agency's mission to protect and promote public health. While the IDE for the Reducer

System was approved, it was clear it would take at least 5 years to complete the study and obtain regulatory approval to bring the Reducer technology to the patients in the US who have limited treatment options for their refractory angina. The Sponsor chose to seek Breakthrough Device Designation for the Reducer which the FDA granted in October 2018, acknowledging the unmet need for these refractory angina patients. Since then, the Sponsor has had several interactive discussions with FDA. Following those meetings, the company filed the PMA for the Reducer System in late 2019. The PMA includes clinical data from the randomized, sham-controlled study (COSIRA) as well as the postmarket observational study (REDUCER-I) and published real-world experience, along with the proposed robust post-approval study (REDUCER-II), to provide the balance between pre- and postmarket clinical evidence needed to support approval of this Breakthrough Device, allowing more timely access to patients with an unmet need.

4.1.1 Breakthrough Designation

The Reducer System was granted Breakthrough Designation on 09 October 2018. Neovasc has worked interactively with FDA through the Breakthrough Devices Program to facilitate the premarket review of the Reducer System. The Breakthrough Devices Program is for certain medical devices that provide for more effective treatment or diagnosis of life-threatening or irreversibly debilitating diseases or conditions. FDA has published guidance on the Breakthrough Devices Program (FDA 2018). This guidance discusses that while these devices must still meet the statutory standard for reasonable assurance of safety and effectiveness, there are several factors to consider when interpreting that standard for breakthrough devices. FDA has also published several other guidance documents that support this framework and they will each be considered below.

As a reference, the FDA standard for safety (21 CFR 860.7(d)(1)) is:

> *There is reasonable assurance that a device is safe when it can be determined, based upon valid scientific evidence, that the probable benefits to health from use of the device for its intended uses and conditions of use, when accompanied by adequate directions and warnings against unsafe use, outweigh any probable risks. The valid scientific evidence used to determine the safety of a device shall adequately demonstrate the absence of unreasonable risk of illness or injury associated with the use of the device for its intended uses and conditions of use.*

The FDA standard for effectiveness (21 CFR 860.7(e)(1)) is:

> *There is reasonable assurance that a device is effective when it can be determined, based upon valid scientific evidence, that in a significant portion of the target population, the use of the device for its intended uses and conditions of use, when accompanied by adequate directions for use and warnings against unsafe use, will provide clinically significant results.*

The FDA's guidance on Balancing Premarket and Postmarket Data Collection for Devices Subject to Premarket Approval (FDA 2015) discusses the right balance of premarket and postmarket data collection to facilitate timely patient access to important new technology without undermining patient safety. The guidance states that when making a determination, it should be considered whether it is appropriate to collect certain data in the postmarket setting, rather than premarket and FDA considers, among other factors, the device's potential impact on public health. The Breakthrough Devices Program guidance (FDA 2018) states that, for PMAs designated as Breakthrough Devices, FDA intends to use timely postmarket data collection, when scientifically appropriate, to facilitate expedited and efficient development and review of the device.

FDA may also approve a device with a greater degree of uncertainty regarding the benefits and risks of the device if this uncertainty is sufficiently balanced by other factors, including the probable benefits of the device and the extent of postmarket controls. As part of the Breakthrough Device Designation described in the FDA Breakthrough Devices Program Guidance (FDA 2018), in order to facilitate earlier patient access to devices that demonstrate the potential to address an unmet medical need, FDA may accept a higher degree of uncertainty about the benefit-risk profile of the device at the time of approval by collecting certain data in the postmarket setting rather than premarket.

In order to help describe what is meant by uncertainty and the FDA's current approaches, the FDA published the guidance document, Considerations of Uncertainty in Making Benefit-Risk Determinations in Medical Device Premarket Approvals (FDA 2019a), which discusses the least burdensome provisions and promoting the public health by fostering medical device innovation and facilitating timely patient access to high quality, safe and effective medical devices. This guidance discusses the type of uncertainty when considering the benefit-risk information. This guidance supports the premarket/postmarket data collection balance concept proposed by FDA by considering the type and amount of postmarket data that may be collected to reduce any remaining uncertainty, indicating that in cases with modest or high uncertainty, that could be supported with modest or substantial postmarket data collection.

Consistent with FDA's guidance document Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approval and De Novo Classifications (FDA 2019b), postmarket data collection is also discussed as a factor FDA considers as a part of making benefit-risk determinations. In this guidance, FDA also states that it is not unusual for novel devices that address an unmet medical need to have relatively small probable benefits, and FDA may determine the novel device to be reasonably safe and effective even though the sponsor demonstrates a relatively small probable benefit. In addition, the development of innovative technology may provide additional future benefits to patients. With subsequent generations of the device, its benefit-risk profile may change (e.g., the benefits may increase or the risks may be reduced), the expected level of safety and effectiveness may change, and later

versions may offer significant advantages over the initial device. In these circumstances, in order to facilitate patient access to new devices important for public health and to encourage innovation, FDA may tolerate greater uncertainty in an assessment of benefit or risk than for most established technologies, particularly when providers and patients have limited alternatives available.

FDA may consider the collection of postmarket data as a way to clarify the magnitude and effect of mitigations or as a way to develop additional information regarding benefits or risks for certain device types or in specific patient populations when making a benefit risk determination. In addition, pursuant to section 513(a)(3)(C) of the FD&C Act, "in certain cases, such as if a device is likely to be denied approval due to uncertainty about its effectiveness, FDA will consider whether postmarket data collection or other conditions might be structured so as to permit approval subject to those conditions." As a designated breakthrough medical device, the following factors should be considered in determining the safety and effectiveness of the Reducer:

- The Reducer System is intended for "no option patients" who are refractory to currently available treatment options.
- The Reducer System is a prescription device, and the labeling will clearly state this is for no option patients, so physicians can ensure patients are true candidates for the device.
- The reduction of CCS class seen in these no option patients is clinically meaningful, and the device has a demonstrated safe profile of use.
- Bench, animal (Konigstein et al 2018b), and human data out to 12 years (Parikh et al 2018) have demonstrated NO device fractures and a robust safety profile.

The Reducer System is also supported by a postmarket experience of more than 2,500 distributed devices with a very low observed reported AE rate. Additionally, a significant amount of supportive clinical evidence demonstrates short- and long-term safety and effectiveness (details are provided in Sections 5.2.2 and 6.6). The COSIRA study and supporting evidence meets the regulatory criteria for reasonable assurance of safety and effectiveness for treating these "no option" patients with the breakthrough designated Reducer device. The Sponsor is committed to conducting a robust randomized, sham-controlled post-approval study to further support the findings in COSIRA (details are provided in Section 7).

4.2 Clinical Development Program

First in Man Study

The first clinical use of the Reducer was in the FIM Study. The FIM Study used the first generation of the Reducer, which was provided unmounted and had to be hand crimped onto the delivery system. As discussed in Section 3.2.1, the differences in the Reducer design between the original and the current device generation are minimal, so FIM data

can be considered informative of the submitted design. There were no distinguishable differences in CT angiography findings between the COSIRA and FIM cohort.

A total of 15 patients were enrolled at 3 investigational sites (2 sites in India and 1 in Germany). The Reducer was successfully implanted in all 15 patients, and there were no major procedure-related AEs (i.e., death, MI, perforation of the CS, total occlusion of the CS, or the need for urgent dilation of the Reducer) during the procedure or the 6-month follow-up period. Proper location, lack of migration, and patency of all implanted Reducers was confirmed by CT angiography at 2 days and 6 months post-implantation. Mean CCS was 3.07 ± 0.47 at baseline and 1.64 ± 0.84 at follow-up (n=14, $p < 0.0001$). During the follow-up period, 12 (86%) patients had ≥ 1 functional CCS class improvement, and 2 (14%) patients had no change in CCS class.

Two long-term follow-up studies were reported on the patients who participated in the FIM Study. The first study included 14 of the 15 original patients at 3 years post-implantation (1 patient was lost to follow-up). There were no deaths, MIs, or AEs attributed to the device. Three patients underwent revascularization (1 CABG, 2 PCI) due to progression of their obstructive CAD. Thirteen patients had ≥ 1 functional CCS class improvement, and 8 of those patients had ≥ 2 functional CCS class improvement, while 1 patient was unchanged compared to baseline. Cardiac CT angiography was performed on 11 patients and confirmed that the Reducer was clearly visible, patent, well-positioned, and located at the exact site of deployment with no evidence of migration or occlusion.

The second long-term follow-up evaluation of 7 patients in the FIM Study was conducted 12 years post-implantation. Additional data from this study are detailed in Sections 5.2.2 and 6.6.

REDUCER-I Observational Study

REDUCER-I is a multi-center, international, 3-arm postmarket observational study that was initiated following a controlled market release of the Reducer to further confirm its long-term safety and effectiveness.

REDUCER-I includes 3 treatment arms:

- Arm 1: This arm includes de novo patients, and data are prospectively collected. These patients with refractory angina pectoris who demonstrate objective evidence of reversible myocardial ischemia, who have limited or no options for revascularization are assessed for Reducer implantation.
- Arm 2: Patients who have received the Reducer in the COSIRA study. This arm includes both retrospective and prospective data collection.
- Arm 3: Patients implanted under CE Mark prior to the REDUCER-I Study. This arm includes both retrospective and prospective data.

REDUCER-I is currently ongoing, with study enrollment anticipated to complete in 2022, and implanted patients will be followed for 5 years. At the time of the interim analysis on 12 March 2020, there have been 241 patients enrolled in the study at 20 study sites. Enrollment by study arm is: 191 patients in Arm 1, 11 patients in Arm 2, and 39 patients in Arm 3. Data on the effectiveness and safety from REDUCER-I are provided in Section 5.2.1 and Section 6.2.1, respectively.

COSIRA

The primary data set supporting the approval of the Reducer is the COSIRA Study, which was a prospective, randomized, double-blind, sham-controlled multi-center study conducted in Canada, Belgium, the UK, the Netherlands, Denmark, and Sweden. Data on the effectiveness and safety from COSIRA are provided in Section 5.1 and Section 6.2, respectively.

5 CLINICAL EFFECTIVENESS

Summary

- The Reducer demonstrated effectiveness in improving life-altering symptoms of patients in COSIRA – a double-blind, randomized, sham-controlled clinical trial – with additional data from a supportive study and substantial, consistent clinical evidence from numerous peer-reviewed publications.
- The primary endpoint was met in COSIRA: 34.6% of patients in the Reducer arm and 15.4% in the Control arm improved by ≥ 2 CCS classes at 6 months (p=0.024), consistent with a clinically significant improvement in angina severity.
- Many of the secondary endpoints provided supportive data on effectiveness of the Reducer; however, the study was not powered to demonstrate statistical significance on these endpoints. Secondary endpoints did not have pre-specified hypothesis tests, and their analyses did not account for multiplicity, therefore, this limitation should be considered when interpreting the results.
    - Of the 50 patients (96.2%) who were successfully implanted with the Reducer, all 50 (100%) were considered to be procedural successes.
    - 71.2% of patients in the Reducer arm and 42.3% of patients in the Control arm improved by ≥ 1 CCS class at 6 months (p=0.003), consistent with a clinically significant improvement in angina severity.
    - The Quality of Life domain on the SAQ showed a statistically significant difference in favor of the Reducer arm.
    - Though not statistically significant, the results for the Reducer arm showed a substantial improvement from baseline on the ETT.
    - In the dobutamine ECHO Modified LCA WMSI (stress) analysis using paired data, the Reducer arm showed a greater decrease from baseline to 6-month follow-up compared with the Control arm.
    - CT angiography performed at 6 months showed no device migration, no fractures, and all devices were patent.
- Steps were taken to ensure patients remained blinded to treatment assignment in COSIRA, including headphones and/or sedatives during the implantation procedure, aseptic draping to cover patients' faces during the procedure, and independent blinded physicians performing CCS and SAQ assessments.
- Data from the REDUCER-I observational study provide supportive evidence of the effectiveness of the Reducer in patients with refractory angina.
    - At 2 years, 81.6% of patients improved by ≥ 1 CCS class and 30.6% improved by ≥ 2 CCS classes. At 5 years, 80.0% improved by ≥ 1 CCS class and 35.0% improved by ≥ 2 CCS classes.
    - The Reducer also improved the functional status of patients with angina as measured by the SAQ, with statistically significant differences between treatment arms favoring the Reducer across all domains at 1 year.
- Published literature with consistent clinical evidence from multiple peer-reviewed publications also supports the effectiveness of the Reducer in refractory angina.

- Overall, the Reducer is effective in improving quality of life for "no option" patients with refractory angina.

5.1 COSIRA Study

5.1.1 Study Design

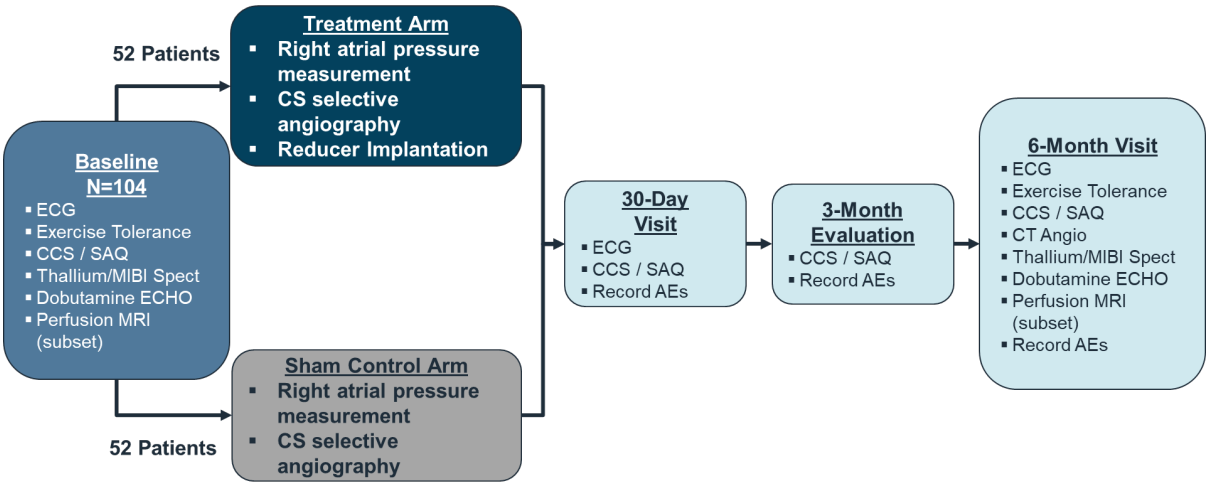
COSIRA was a prospective, multi-center, randomized, double-blind, sham-controlled study designed to evaluate the safety and effectiveness of the Reducer in patients with refractory angina who demonstrated evidence of reversible ischemia but who had limited treatment options (Figure 14). A total of 104 patients were enrolled at 11 centers, with 52 patients in each study arm.

Patients who underwent screening and met the enrollment criteria, including angiographic screening criteria, were randomized into the study. For the angiographic screening, patients had a right atrial pressure measurement and CS selective angiography as the last screening test. Patients who met the angiographic inclusion criteria (details provided in Section 5.1.1.2) were randomized to the Reducer or Control arm. Patients in the Reducer arm were implanted with the device, and the angiographic screening procedure was used as the sham-control for patients randomized to the control arm.

All patients enrolled and randomized were placed on acetylsalicylic acid (Aspirin) and clopidogrel or prasugrel (if not already taking them) for the duration of the clinical study unless contraindicated. Patients who were randomized to the Reducer group received heparin or bivalirudin once randomized and prior to the Reducer implantation unless contraindicated.

Patients were followed for 6 months with assessments at Day 30, Month 3, and Month 6. Patients at one site (n=4) were followed for 1 year due to local regulatory requirements. Effectiveness measures included CCS assessment, dobutamine ECHO, SAQ, and ETT. Details on these measures are provided in Section 5.1.1.3.

Figure 14: COSIRA Study Design



Note: Independent, blinded physicians performed pre- and post-procedure CCS and SAQ assessments
Note: Adapted from Verheye, S et al. N Engl J Med Feb 5, 2015 2015; 372:519-527

Study oversight included a CEC and DSMB. The CEC comprised 3 interventional cardiologists who reviewed and adjudicated all AEs. The DSMB comprised 4 cardiologists with relevant clinical experience who monitored patient safety and the scientific integrity of the study.

5.1.1.1 Maintaining Blinding

The following steps were taken to maintain blinding:

- Patients 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.
- As mentioned above, both Reducer and Control group patients were pre-treated with dual antiplatelet therapy and continued on this for 6 months.
- The treatment assignment (opening of the treatment randomization envelopes) was revealed outside of the procedure room, and the content of the randomization envelope (i.e., “Reducer” or “No treatment”) was read silently and was never spoken. After the content of the envelope was seen by the operator, the physicians returned to the procedure room.
- Implanting physicians were instructed to behave in the same manner with both Control and Reducer group patients (e.g., mimicked the Reducer implant procedure in the Control group; including movement of the catheterization laboratory table, obtaining jugular access, conducting coronary sinus angiography and advancement of the guidewire and the multi-purpose catheter into the CS).

- Patients wore headphones with music and/or were given intravenous sedatives to aid in blinding by preventing the patient from hearing the physicians' discussions throughout the procedure.
- Patients were aseptically draped to cover their faces so they could not see any of the activities in the room.
- Independent, blinded physicians performed the pre- and post-procedural CCS assessments and SAQ for patients in both arms.
- Dobutamine ECHO and ETT core laboratories were also blinded to treatment assignments.

The results from COSIRA support that the blind was maintained, as is discussed in Section 5.1.7.

5.1.1.2 Enrollment Criteria

Key eligibility criteria included:

1. > 18 years old
2. Symptomatic CAD with chronic refractory angina pectoris classified as CCS class III or IV despite attempted optimal medical therapy for 30 days prior to screening
3. Limited treatment options for revascularization by CABG or PCI, as determined by the investigator
4. Reversible ischemia of the left coronary arterial system

Key exclusion criteria included:

1. Recent (within 3 months) acute coronary syndrome
2. Recent (within 6 months) successful PCI or CABG
3. Unstable angina (recent onset angina, crescendo angina, or rest angina with ECG changes) during the 30 days prior to screening
4. De-compensated congestive heart failure (CHF) or hospitalization due to CHF during the 3 months prior to screening
5. Life-threatening rhythm disorders or any rhythm disorders that would require placement of an internal defibrillator and/or pacemaker
6. Patient with pacemaker or defibrillator electrode in the right atrium, right ventricle, or CS

After meeting initial enrollment criteria, patients were excluded based on the following key angiographic exclusion criteria:

1. Mean right atrial pressure higher than or equal to 15 mmHg
2. Patient with anomalous or abnormal CS as demonstrated by angiogram
    a. Abnormal CS anatomy (e.g., tortuosity, aberrant branch, persistent left superior vena cava); and/or
    b. CS diameter at the site of planned Reducer implantation less than 9.5 mm or greater than 13 mm

A full list of inclusion and exclusion criteria is provided in Appendix 10.1.

5.1.1.3 Effectiveness Endpoints

The primary effectiveness endpoint was a decrease in ≥ 2 CCS classes from baseline to 6-month post-procedural evaluation in Reducer and Control arms. The CCS Angina Grading Scale is detailed in Section 2.2.1.

Secondary effectiveness endpoints included the following evaluations:

- Technical success, defined as successful delivery and deployment of the Reducer to the intended site as assessed by the investigator.
- Procedural success, 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.
- Percentage of patients with a decrease of ≥ 1 CCS class from baseline to 6 months in Reducer vs Control.
- Change from baseline to 6 months in dobutamine ECHO WMSI in Reducer vs Control arms.
- Change from baseline to 6 months in SAQ Score in Reducer vs Control arms.
- Change from baseline to 6 months in Total Exercise Duration, Time to 1 mm ST Segment Depression, Maximal ST Segment Depression, Metabolic Equivalents of Task, and Double Product by ETT.

Core laboratories were used to standardize interpretation of data from wall motion score index by dobutamine ECHO WMSI, ETT, and CT angiography (additional analysis in Section 5.1.5.1).

5.1.1.4 Statistical Analyses

Sample Size

The sample size for the COSIRA study was planned to provide an adequate degree of power (80%) to test the primary effectiveness endpoint at the pre-specified, two-sided alpha level of 0.05. Based on a literature review, 40% of patients in the Reducer arm

and 15% of patients in the Control arm were expected to exhibit an improvement of ≥ 2 CCS classes at 6 months. The planned sample size was 124 patients, with 56 patients per arm and an additional 10% to account for discontinuations. Due to the longer than expected time to complete full enrollment and the better than expected drop-out/lost to follow-up rate, the Sponsor elected to stop enrollment after 104 patients were enrolled. The study was not statistically powered to establish improvement based on the secondary endpoint measures.

Missing Data

The statistical analysis of the primary endpoint used the ITT population. Patients who died prior to the 6-month post-procedural evaluation were counted as failures unless adjudicated by the CEC that the cause of death was non-cardiovascular and could not have been attributed to the device or procedures. There was 1 missing 6-month evaluation, which was due to death for reasons unrelated to the study that was imputed as a failure. Drop-outs were included in the analyses using the available data. All patients with available data were used for the analyses. For the secondary endpoint analyses, patients with missing data had their last known observation carried forward (LOCF) for the study endpoints in the effectiveness analysis.

Multiple methods for missing data imputation were performed for the secondary endpoints including last known observation carried forward (LOCF), multiple imputation and tipping point analyses. Multiple imputation models were employed for each outcome to account for variability in imputed values, and results from multiple imputed datasets were combined allowing for valid statistical inferences. The pre-specified subgroup variables were used in the model and included: baseline left ventricular ejection fraction, previous CABG, diabetes, sex, age, race, and study site. Randomization arm and baseline score for each outcome were also included to inform the imputation process, as well as 30-day and 3-month scores for the SAQ analysis.

Tipping point analyses were also conducted on the ITT cohort to present all possible scenarios if the best or worst case was imputed for each missing value. Overall observed minimum and maximum values were used for imputation.

Analysis Populations

The ITT population (n=104) included all patients who signed the written informed consent, were considered to meet the study entry criteria, and were randomized to a study arm.

The Per-Protocol (PP) population (n=102) only included patients who completed the study. Patients who did not complete the study or were randomized to the Reducer arm but did not receive a device due to technical failure (i.e., 2 patients) were not analyzed in the PP population. The patients who did not have a Reducer implanted but were still blinded were added to the Control arm in the “as-treated” population.

The Safety population included all randomized patients (n=104). All safety analyses evaluated patients according to actual treatment received and were performed using the Safety population, which is equivalent to the “as-treated” population.

Primary Endpoint Analyses

A patient met the primary endpoint criteria if he or she had a reduction of ≥ 2 classes in CCS classification from the baseline screening to the 6-month post-procedural evaluation. The Pearson chi-square test without continuity correction was used to compare the difference between the proportion of patients meeting the primary endpoint criteria in the Reducer and Control arms; since the expected cell values were all greater than 5, the continuity correction was not deemed necessary. The p-value threshold for the primary endpoint ITT analysis was set at 0.0469 (instead of 0.05) due to the interim analysis that was performed.

Secondary Endpoint Analyses

Binary endpoints (i.e., ≥ 1 CCS class improvement) were compared between study arms using the Pearson chi-square test or Fisher’s exact test with a two-sided 0.05 level of significance. Continuous endpoints (i.e., dobutamine WMSI, SAQ, ETT) were compared between study arms using Student’s t-test or the Wilcoxon rank sum test, depending on distribution of data.

The study was not statistically powered to establish improvement in angina by these secondary endpoint measures. Secondary endpoint analyses were not pre-specified and did not account for multiplicity.

Interim Analysis

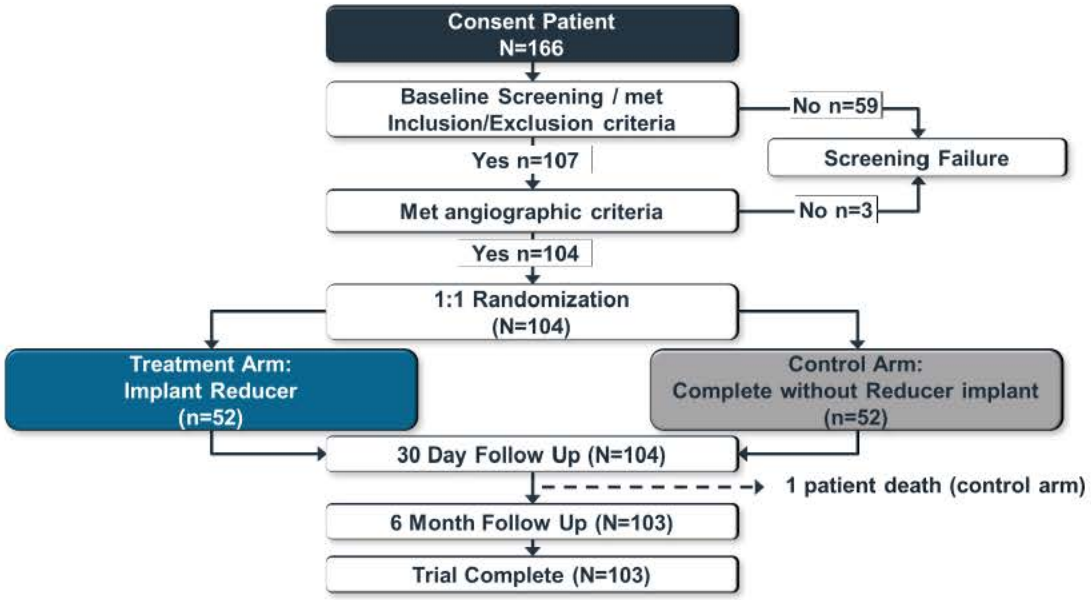
An interim analysis was planned for the primary effectiveness endpoint after 50% of the cohort (62 patients) completed their 6-month follow-up visit. The interim analysis was planned to evaluate the potential early stopping (based on a Lan-DeMets approach with an O’Brien-Fleming spending function), as well as the conditional power. An independent DSMB was tasked with reviewing the interim analysis. The trial was not stopped based on the interim analysis.

5.1.2 Patient Disposition and Baseline Characteristics

5.1.2.1 Patient Disposition

A total of 166 patients were screened, and 104 were randomized into the study (52 in each arm) (Figure 15). The most common reason for screening failure was a negative dobutamine stress ECHO (58.1%). Only one patient did not complete the study, which was due to death for reasons unrelated to the study. There were no patients who withdrew consent or were lost to follow-up.

Figure 15: COSIRA: Patient Disposition



5.1.2.2 Baseline Demographics and Medical History

Baseline demographics were generally well balanced between study arms (Table 5). The average age of patients was approximately 68 years old, and the majority of patients were male and White.

Table 5: COSIRA: Baseline Demographics

Baseline Characteristics	Reducer N=52	Control N=52
Age (years), mean (range)	69.6 (51–87)	66.0 (35–84)
Male – n (%)	44 (84.6)	40 (76.9)
White – n (%)	44 (84.6)	46 (88.5)
Weight (kg), mean	84.9	85.0
Heart Rate (bpm) mean	64.9	65.4
Systolic Blood Pressure (mmHg), mean	128.1	131.1
Diastolic Blood Pressure (mmHg), mean	68.0	70.6

Baseline medical history was also relatively well balanced between study arms (Table 6). There were fewer patients with diabetes in the Reducer arm than the Control arm, but the study arms were comparable in terms of smoking history, hypercholesterolemia, hypertension, and family history of cardiovascular disease.

Table 6: COSIRA: Baseline Medical History

	Reducer N=52 n (%)	Control N=52 n (%)
Diabetes mellitus	21 (40.4)	25 (48.1)
Smoking of cigarettes		
Previous smoker	22 (42.3)	24 (46.2)
Current smoker	5 (9.6)	7 (13.5)
Hypercholesterolemia	50 (96.2)	46 (88.5)
Hypertension	42 (80.8)	41 (78.8)
Family history of cardiovascular diseases	39 (75.0)	37 (71.2)
Valve disease	2 (3.8)	4 (7.7)
Present or recurrent arrhythmias	10 (19.2)	12 (23.1)
Other vascular diseases		
Peripheral vascular disease	6 (11.5)	8 (15.4)
Previous stroke	1 (1.9)	4 (7.7)
Previous MI	27 (51.9)	30 (57.7)
Previous PCI	36 (69.2)	40 (76.9)
Previous CABG	42 (80.8)	38 (73.1)

All patients had a CCS class of III or IV at baseline, as required for patients to be enrolled in COSIRA (Table 7).

Table 7: COSIRA: Baseline CCS Class

	Reducer N=52 n (%)	Control N=52 n (%)
CCS Class III	42 (80.8)	45 (86.5)
CCS Class IV	10 (19.2)	7 (13.5)

Table 8 shows baseline cardiovascular medications taken within 30 days prior to the procedure. All patients in both study arms were taking cardiovascular medications as directed in the protocol, and the majority were taking ASA/Aspirin (anti-platelets), beta-blocker, and/or statins.

Table 8: COSIRA: Baseline Cardiovascular Medications

	Reducer N=52 n (%)	Control N=52 n (%)
Patients Taking Cardiac Medication	52 (100.0)	52 (100.0)
ASA (Aspirin)	48 (92.3)	48 (92.3)
Statins	48 (92.3)	45 (86.5)
Beta-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)
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)
Ranolazine	2 (3.8)	2 (3.8)
Prasugrel	1 (1.9)	3 (5.8)
Digitalis/digoxin	1 (1.9)	0 (0)

5.1.3 Primary Endpoint Results: ≥ 2 CCS Class Improvement

COSIRA met the primary effectiveness endpoint, with a significantly greater proportion of patients in the Reducer arm having an improvement of ≥ 2 CCS classes from baseline to 6 months compared with the Control arm in the ITT population (p=0.024) (Table 9). The NNT for a 2 CCS class improvement was 5.2 patients.

Table 9: COSIRA: Percentage of Patients with ≥ 2 CCS Class Improvement at 6 Months (ITT Population)

CCS Class Change from Baseline	Reducer N=52 % (n/N) [95% CI]	Control N=52 % (n/N) [95% CI]	Difference (Reducer – Control) [95% CI]	p-value	NNT [95% CI]
≥ 2 Class CCS Improvement	34.6% (18/52) [21.7%, 47.5%]	15.4% (8/52) [5.6%, 25.2%]	19.2% [3.0%, 35.5%]	0.024	5.2 [2.8, 33.3]

Note: P-value based on Pearson Chi-square test.

An additional "as-treated" analysis was performed, which included in the Control arm the 2 patients who were randomized into the Reducer arm but did not have a device implanted. The results of this analysis were consistent with the ITT population; significantly more patients in the Reducer arm experienced a decrease of ≥ 2 CCS classes from baseline to 6 months compared with the Control arm (p=0.013) (Table 10).

Table 10: COSIRA: Percentage of Patients with ≥ 2 CCS Class Improvement at 6 Months ("As-Treated" Population)

CCS Class Change from Baseline	Reducer N=50	Control N=54	Difference (Reducer – Control) [95% CI]	p-value	NNT [95% CI]
≥ 2 Class CCS Improvement	36.0% (18/50) [22.7%, 49.3%]	14.8% (8/54) [5.3%, 24.3%]	21.2% [4.9%, 37.5%]	0.013	4.7 [2.7, 20.6]

Note: Categorical Data are presented as % (n/N) [95% CI]. P-value based on Pearson Chi-square test.

5.1.3.1 Subgroup Analysis

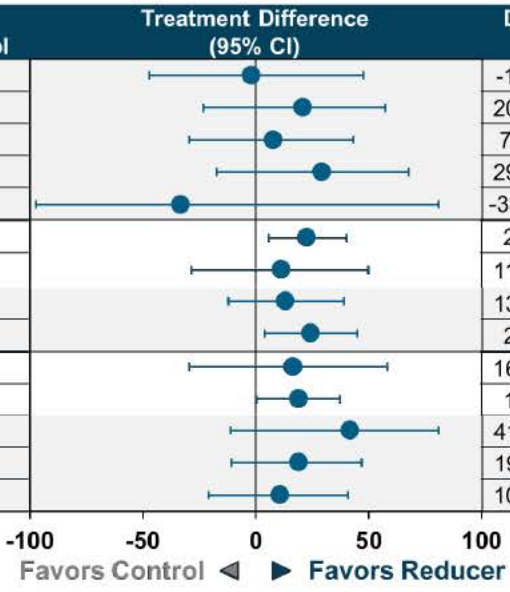
The following subgroups were pre-specified to examine the primary endpoint stratified according to:

- Baseline left ventricular ejection fraction (20–40, 41–50, 51–60, 61–70, 71–90)
- Previous CABG
- Diabetes
- Sex
- Age (30–60, 61–70, 71–90)
- Race
- Study Site

Hypothesis tests were not formally evaluated and no type-1 error adjustments for multiple comparisons were incorporated. Based on the interaction p-values and consistent direction favoring the Reducer group over Control, there is no evidence to suggest the treatment effect differs by subgroup (Figure 16).

Figure 16: COSIRA: Proportion of Patients with ≥ 2 CCS Class Improvement by Subgroup

Subgroup	Subgroup	Reducer	Control	Difference (%) [95% CI]	Interaction P-Value
Baseline LVEF	20-40%	13%	14%	-1.8 [-47.2, 47.2]	0.802
	41-50%	30%	9%	20.9 [-23.4, 57.0]	
	51-60%	35%	27%	7.7 [-29.6, 43.0]	
	61-70%	38%	8%	29.2 [-17.6, 67.6]	
	71-90%	0%	33%	-33.3 [-97.5, 80.9]	
Previous CABG	Yes	33%	11%	22.8 [5.5, 40.1]	0.383
	No	40%	29%	11.4 [-28.6, 49.8]	
Diabetes	Yes	33%	20%	13.3 [-12.2, 38.9]	0.426
	No	36%	11%	24.4 [3.8, 45.0]	
Sex	Female	25%	8%	16.7 [-29.4, 58.1]	0.829
	Male	36%	18%	18.9 [0.4, 37.3]	
Age (years)	30-60	50%	8%	41.7 [-11.5, 80.7]	0.494
	61-70	35%	16%	19.0 [-11.0, 46.6]	
	71-90	31%	20%	10.8 [-21.0, 40.7]	



5.1.4 Secondary Endpoint Results

5.1.4.1 Technical and Procedural Success

Reducer Technical Success

The Reducer was successfully implanted in 50 (96.2%) of 52 patients. In both instances where there was a technical failure, failure to implant the Reducer was due to anatomical variations not known during screening and was not due to device design and/or performance.

Reducer Procedural Success

Of the 50 patients who were successfully implanted with the Reducer, all 50 (100%) were considered to be a procedural success. None of the 50 patients exhibited an Adverse or Serious Adverse Device Effect requiring a clinically-driven intervention.

5.1.4.2 ≥ 1 CCS Class Improvement

The difference between the proportion of patients experiencing an improvement of ≥ 1 CCS classes from baseline to 6 months in the Reducer and Control arms in the ITT population was statistically significant in favor of the Reducer arm (p=0.003) (Table 11). The NNT for a 1 CCS class improvement was 3.5.

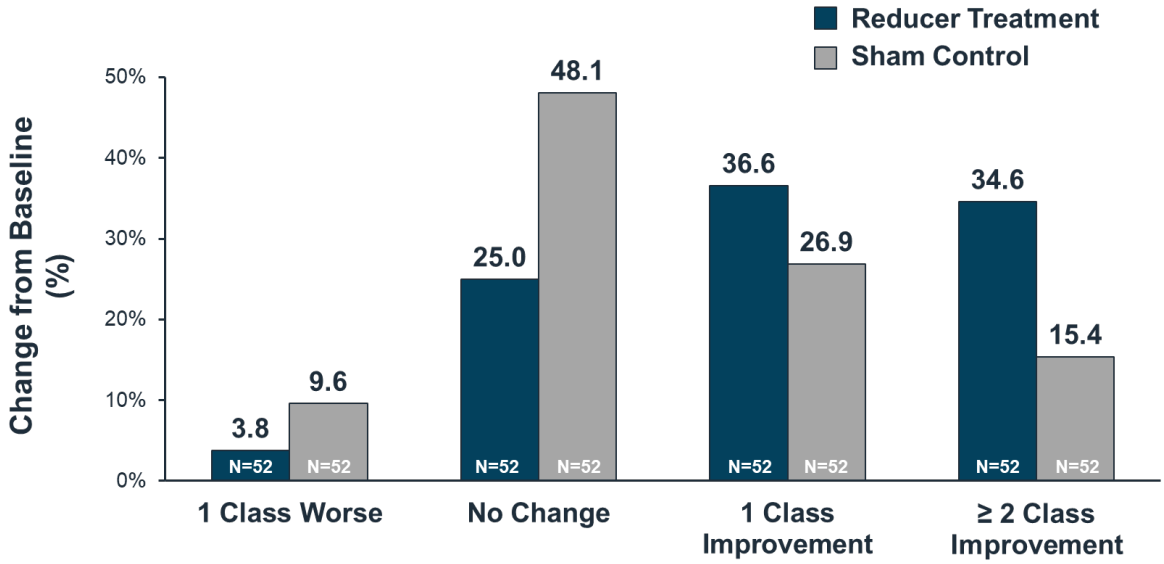
Table 11: COSIRA: Percentage of Patients with ≥ 1 CCS Class Improvement at 6 Months (ITT Population)

CCS Class Change from Baseline	Reducer N=52 % (n/N) [95% CI]	Control N=52 % (n/N) [95% CI]	Difference (Reducer – Control) [95% CI]	p-value	NNT [95% CI]
≥ 1 Class CCS Improvement	71.2% (37/52) [58.8%, 83.5%]	42.3% (22/52) [28.9%, 55.7%]	28.8% [10.6%, 47.1%]	0.003	3.5 [2.1, 9.4]

Note: p-value based on Pearson Chi-square test.

At baseline, all patients had CCS class III or IV; 36.5% of patients in the Reducer arm had a 1 class improvement and 34.6% had a ≥ 2 class improvement at 6 months, compared with 27.4% and 15.7% in the Control arm, respectively (Figure 17).

Figure 17: COSIRA: Distribution of Change in CCS Class at Month 6 (ITT Population)



Note: Does not include 1 patient who died prior to 6 months.

5.1.4.3 Dobutamine ECHO WMSI

In the dobutamine ECHO WMSI analysis using paired data, Modified LCA WMSI (stress) results showed a decrease in WMSI (baseline to 6-month follow-up) in favor of the Reducer arm over the Control arm. The mean decrease from baseline was 0.18 (12.33%) in the Reducer arm and 0.09 (6.56%) in the Control arm (p=0.346). The Reducer arm showed similar improvement as the Control arm on the Resting WMSI, Resting Modified Left Coronary Artery (LCA), and Stress WMSI, and the differences between study arms were not statistically significant.

5.1.4.4 Seattle Angina Questionnaire

The Reducer arm showed statistically significant improvement in Quality of Life scores on the SAQ (p=0.048). Results for Physical Limitations, Anginal Stability, and Anginal Frequency showed improvements from baseline in favor of the Reducer arm but did not reach statistical significance.

5.1.4.5 Exercise Tolerance Test

On the ETT, there was improvement in total exercise duration, time to 1 mm ST segment depression, and maximal ST segment depression with the Reducer, but these differences did not reach statistical significance. Though not statistically significant, the results for the Reducer arm showed a substantial improvement from baseline; exercise duration in the Reducer arm improved, with a mean increase of 64.68 seconds vs. 4.3 seconds in the Control arm – an increase of 15 times more, on average, than in the Control arm.

5.1.5 Additional Analyses

5.1.5.1 CT Angiography

CT angiography was performed at 6 months for 37 subjects in the Reducer group only. In 37/37 patients (100%), the Reducer was located in the coronary sinus and showed no signs of migration. In 35 of 37 patients (94.6%), contrast flow could be seen in the Reducer, demonstrating that the device was patent. In the patients where flow was not seen through the Reducer, it was determined that the imaging and opacification of the study were not optimal and led to this reporting.

In 16 of 37 (43.2%) patients it was reported that thrombus was present in the Reducer. Of the patients with thrombus reported, none were 100% occluded and only 2 showed a luminal narrowing of more than 50%. However, the number of patients for whom thrombus was reported may be exaggerated. The CT Angio Core Lab determined when examining the CT angiograms for thrombus, to refer to areas of low CT density on the device as thrombus from a coding standpoint.

CT Angiography Retrospective Analysis

Neovasc submitted an IDE to FDA in 2016, during interactive discussions a decision was made to have a retrospective analysis of the COSIRA CTAs done by the same CT Core Lab to address concerns related to device patency/occlusion, embolization/thrombus, as well as fracture/durability. FDA provided specific direction regarding the data and format to be provided. Following the analysis, data were submitted to FDA. This retrospective analysis confirmed that there were no device fractures and all devices were patent. Thirteen devices demonstrated hypoattenuation (defined as intimal proliferation), consistent with intimal proliferation typically seen in coronary artery stents. Dr Gaby Weissman from the CT Angio Core Lab previously noted that CT angiography cannot accurately differentiate thrombus, substantial thrombus, fibrosis, or beam hardening.

5.1.6 Sensitivity Analyses

Sensitivity analyses were performed for the secondary endpoints; however, hypothesis tests were not pre-specified for these endpoints, and conclusions are considered exploratory. Two missing data imputation methods were performed for the secondary effectiveness endpoints where LOCF was initially implemented. Multiple imputation models were employed for each outcome to account for variability in imputed values, and results from multiple imputed datasets were combined allowing for valid statistical inferences.

Tipping point analyses were also conducted on the ITT cohort to present all possible scenarios if the best or worst case was imputed for each missing value. Best- and worst-case imputed values were based on the extreme values for the observed change for the endpoint. The best-case scenarios were based on the most favorable imputation for characterizing the treatment effect of Reducer compared to Control, and worst-case

scenarios were based on the least favorable imputation for characterizing the treatment effect.

Tipping point analysis results for dobutamine ECHO WMSI showed some sensitivity to the pattern of missing data with worst-case scenarios showing a significant difference in favor of Control.

Tipping point analysis results for SAQ showed no significant differences between randomized groups for Physical Limitations, Anginal Frequency, and Treatment Satisfaction scores. The Reducer group had a significant improvement compared to Control in the best-case scenarios for Anginal Stability and Quality of Life.

Tipping point analysis results for total exercise duration showed some sensitivity to the pattern of missing data with worst-case scenarios showing a significant difference in favor of Control.

5.1.7 Evidence of the Blind Maintained

While there was no blinding questionnaire in the study, the CCS Class data in Table 12 support that the blinding was maintained as the CCS Class improvement at 30 days is similar between both groups, where there is a marked difference at 3 months. This finding would be expected since the period for tissue ingrowth of the Reducer and the establishment of a pressure gradient typically takes 4-6 weeks to produce an effect. Additionally, the presence of a notable placebo effect in the Control arm strongly indicates that the blinding process in the COSIRA trial was real and effective.

Table 12: COSIRA: Improvement in CCS Class Over Time – Observed Data (ITT Population)

Outcome	Visit	Reducer	No Treatment	p-value[1]
Improvement in ≥ 1 CCS Class	30 Day	50.0% (26/52)	43.1% (22/51)	0.4851
	3 Month	76.9% (40/52)	56.9% (29/51)	0.0304
	6 Month	71.2% (37/52)	43.1% (22/51)	0.0041
Improvement in ≥ 2 CCS Class	30 Day	13.5% (7/52)	11.8% (6/51)	0.7954
	3 Month	28.8% (15/52)	15.7% (8/51)	0.1088
	6 Month	34.6% (18/52)	15.7% (8/51)	0.0270

[1] P-values at individual time points are post-hoc and not adjusted for multiple comparisons.
Note: 3-month data/analysis not previously submitted to, nor reviewed by, FDA.

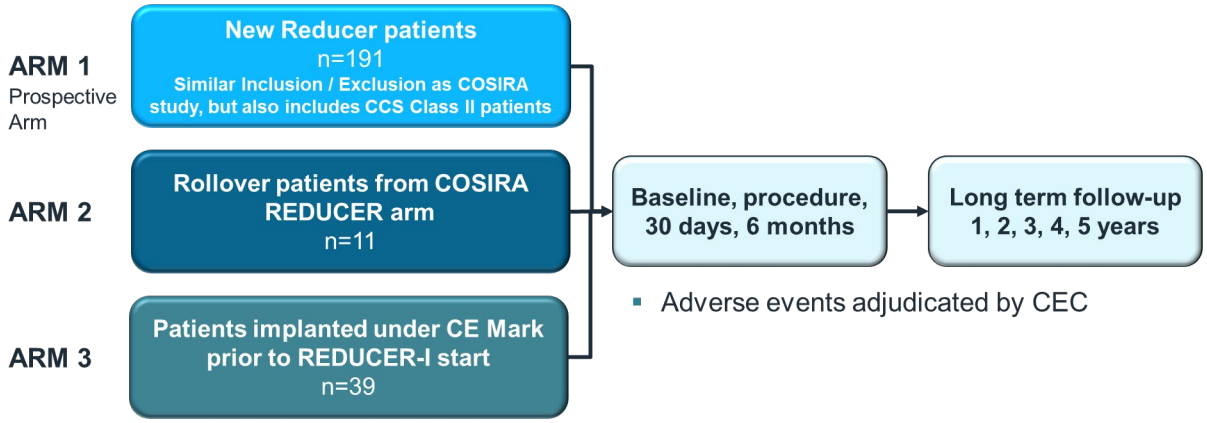
5.2 Additional Supporting Data

5.2.1 REDUCER-I Observational Study

REDUCER-I is an ongoing multi-center, international, 3-arm, postmarket observational study in patients with refractory angina pectoris who demonstrate objective evidence of reversible myocardial ischemia, who have limited or no options for revascularization and are implanted with the Reducer in the REDUCER-I study (Arm 1), or who have received the Reducer in the COSIRA study (Arm 2) or under CE Mark (Arm 3) prior to the

REDUCER-I study (Figure 18). The primary effectiveness endpoint in REDUCER-I is the percentage of patients who experience improvement in their angina symptoms, defined as a reduction in CCS class at 6 months compared to baseline. Primary safety endpoints are discussed in Section 6.3.

Figure 18: REDUCER-I Study Design



At the time of the interim analysis on 12 March 2020, there have been 241 patients enrolled in the study: 191 patients in Arm 1, 11 patients in Arm 2, and 39 patients in Arm 3. Overall, 182 (75.5%) patients are in active follow-up and 59 have exited the study. A total of 158 patients completed the 1-Year Visit, 111 completed the 2-Year Visit, 58 completed the 3-Year Visit, 32 completed the 4-Year Visit, and 23 completed the 5-Year Visit. Table 13 summarizes baseline demographics and medical history of all enrolled patients in each study arm.

Table 13: REDUCER-I: Baseline Demographics and Medical History

Baseline Characteristics		Arm 1 (Prospective) N-91	Arm 2 (COSIRA Follow-up) N=11	Arm 3 (CE Mark) N=39
Age (years), mean ± SD		68.5 ± 9.6	63.2 ± 9.0	67.9 ± 9.9
Male – n (%)		156 (81.7)	10 (90.9)	27 (69.2)
Previous	Myocardial Infarction	97 (51.3)	6 (54.5)	19 (48.7)
	PCI	135 (71.4)	6 (54.5)	28 (71.8)
	CABG	150 (79.4)	8 (72.7)	31 (79.5)
CCS Class	I	0	0	2 (6.3%)
	II	60 (31.9)	0	6 (18.8)
	III	117 (62.2)	9 (81.8)	20 (62.5)
	IV	11 (5.9)	2 (18.2)	4 (12.5)
Diabetes		83 (43.9)	4 (35.4)	20 (51.3)
Current or Previous Smoker		119 (63.0)	7 (63.6)	21 (53.8)
Hypercholesteremia		162 (85.7)	11 (100)	35 (89.7)
Hypertension		154 (81.5)	11 (100)	32 (82.1)

The primary effectiveness endpoint in REDUCER-I is the percentage of patients who experience improvement in their angina symptoms defined as a reduction in CCS class. There were no pre-specified hypothesis tests; p-values presented are not adjusted for multiple comparisons. There was improvement in mean CCS class following treatment with the Reducer, with the trend holding through 5 years. Improvement in ≥ 1 CCS class was observed in 81.6%, and ≥ 2 CCS classes in 30.6% of patients at 2 years (n=98) (Table 14). At baseline, 70.8% of patients had severe disabling angina (CCS class III–IV). After treatment, only 18% suffered from CCS class III–IV at 5 years (Figure 19). Most of these patients with severe angina (CCS class III–IV) became asymptomatic or only mildly symptomatic (CCS class I–II). These findings were similar in patients with only CCS class III and IV at baseline (Figure 20).

Table 14: REDUCER-I: Improvement in CCS Grade from Baseline over Time (All Patients)

CSS Class Change from Baseline	6 Months N=181	12 Months N=140	2 Years N=98
Worsening from baseline	4 (2.2%)	2 (1.4%)	1 (1.0%)
No change from baseline	51 (28.2%)	34 (24.3%)	17 (17.3%)
≥ 1 Class improvement	126 (69.6%)	104 (74.3%)	80 (81.6%)
≥ 2 Class improvement	44 (24.3%)	36 (25.7%)	30 (30.6%)

Figure 19: REDUCER-I: Percentage of Patients with Class III/IV Over Time (All Patients)

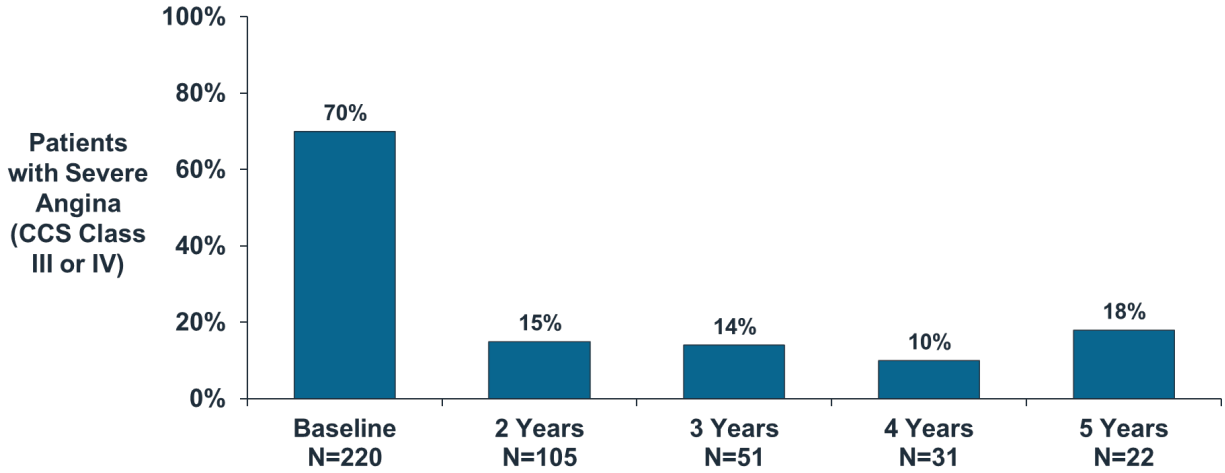
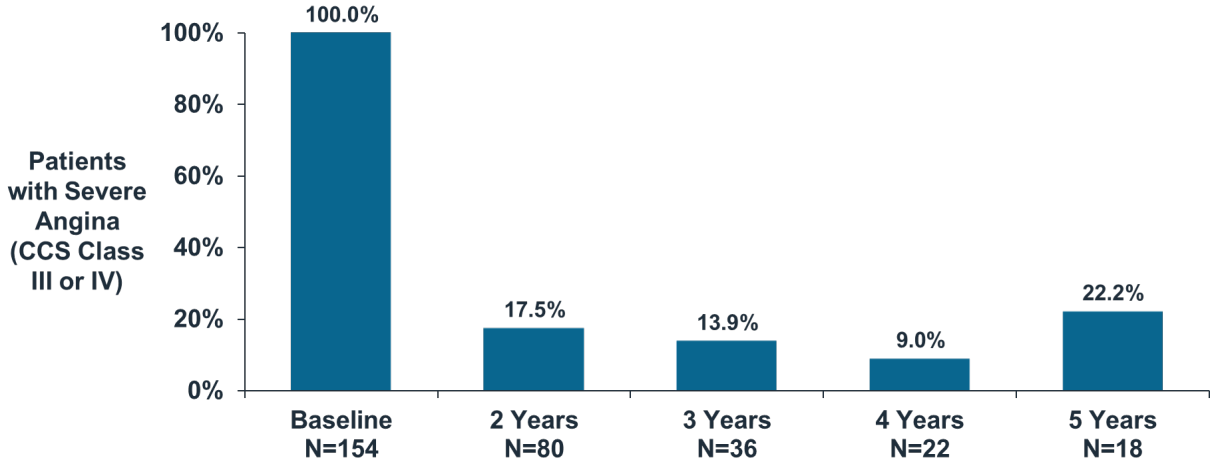


Figure 20: REDUCER-I: Percentage of Patients with Class III/IV Angina Over Time (Only Patients with CCS Class III or IV at Baseline)



Secondary endpoints suggest consistent long-term benefit of the Reducer. The change from baseline on the SAQ was improved across all domains through 1 year ($p < 0.0001$ for all comparisons), with all domains favoring the Reducer at 3 years despite the small sample size (n=24). The EQ-5D-5L, a standardized measure of health status, was included as a secondary endpoint measure in REDUCER-I. There were improvements in nearly all dimensions of the EQ-5D-5L at 6 months (Mobility, Self-Care, Usual Activities, Pain/Discomfort, and Anxiety/Depression) and 1 year (Mobility, Usual Activities, Pain/Discomfort, and Anxiety/Depression), with sustained improvement in Usual Activities and Pain/Discomfort at 24 months. Patients' own global rating of their overall health on the EQ-VAS was also improved at 6, 12, and 24 months.

Improvement in exercise duration on the ETT was observed at 1 year (p=0.0016). REDUCER-I also included the 6MWT, which showed a mean increase from baseline in walking distance of 26 meters at 1 year (p < 0.0019).

In REDUCER-I, the number of documented emergency department visits for angina was also collected for patients in Arm 1 for the 1 year prior to baseline compared to the 1 year after the Reducer implant procedure. Emergency department visits were lower 1 year post-implant (22 visits) compared to baseline (78 visits; p < 0.0001) (Table 15).

Table 15: REDUCER-I: Number of Documented Emergency Department Visits – Arm 1[1] (Paired Data)

Emergency Department Visits	Baseline	1 Year	p-value
Average number of visits including patients with 0 visits[2]	0.69 ± 1.06 (113) [0, 5]	0.19 ± 0.60 (113) [0, 4]	< 0.0001[3]
Patients with ≥ 1 visit[4]	47 (41.6%)	15 (13.3%)	
Total number of visits, all patients	78	22	

[1] Based on patients with baseline and 12 Month Visits; excluding 1 patient with 15 visits at baseline
[2] Data are presented as mean ± SD (N) [min, max]
[3] Based on a Wilcoxon Signed Rank test
[4] Data are presented as % (n/N)

5.2.2 Efficacy Findings in Published Literature

Long-Term Efficacy

The long-term efficacy of the Reducer is supported by published results from an Investigator-initiated study that evaluated patients from the FIM Study (Parikh et al 2018). This 12-year follow-up was conducted at a single center in India that had participated in the Reducer System FIM Study, and included CT angiography imaging to evaluate the location of the Reducer within the CS and to rule out migration and occlusion of the Reducer. The primary outcome at 12 years was confirmation of the position, integrity, and patency of the Reducers by CT angiography. Follow-up CT angiography results were analyzed both by the medical center and by an independent core laboratory and were compared with CT angiography performed 6 months post-Reducer implantation. Secondary outcomes were improvement in angina class and prevalence of MACE. Safety findings from this study are presented in Section 6.6.

At 12 years, all 7 patients reported sustained improvement of angina class compared with baseline status. Six patients had ≥ 1 CCS class reduction, and 4 of these patients had ≥ 2 CCS class reduction, with a mean CCS class reduction of 1.7 ± 0.76 at 12 years follow-up versus 3.14 ± 0.38 at baseline (p=0.01). One patient was alive and clinically well at the data cutoff date but did not participate in the 12-year follow-up.

Additional Published Literature

The Sponsor conducted a review of Reducer literature in studies at multiple centers in Europe and Israel to further compare patient outcomes of safety and effectiveness in the "real-world" with the COSIRA data. Publications with fewer than 40 patients were

not considered for comparison due to the small sample size. There may be overlap in the data reported across publications, which is not able to be confirmed.

The percentage of patients with ≥ 2 and ≥ 1 CCS class improvement after treatment with the Reducer for refractory angina (i.e., responders) are similar to those seen in COSIRA, where 34.6% and 71.2% of patients improved by ≥ 2 and ≥ 1 CCS classes, respectively. The percentage of non-responders (i.e., patients who did not improve with treatment) in the Reducer arm was 28.8%.

As summarized in Table 16 and Table 17, Reducer studies have had a similar percentage of improvement in CCS class, confirming the COSIRA results.

Table 16: ≥ 2 CCS Class Improvement in Published Reducer Studies

Study	N	%
COSIRA Treatment Arm	18/52	34.6
Konigstein, EuroIntervention (2018a)	19/39	48
Giannini, JACC (2018b)	20/50	40
Giannini Int J Card (2018a)	63/141	45
D'Amico GISE (2019)	183	50
Ponticelli Int J Card 2019 (2019)	16/42	35.6

Table 17: ≥ 1 CCS Class Improvement in Published Reducer Studies

Study	N	%
COSIRA Treatment Arm	37/52	71.3
Konigstein, EuroIntervention (2018a)	33/39	85
Giannini, JACC (2018b)	40/50	80
Giannini Int J Card (2018a)	141	81
D'Amico GISE (2019)	183	83.3
Ponticelli Int J Card (2019)	34/42	75.6

Results from the SAQ in published literature provide additional support of the Reducer for the treatment of refractory angina. Although COSIRA was only statistically significant for the domain of Quality of Life when comparing the treatment group to the Control group, the referenced articles show statistical significance in every domain of the SAQ (Table 18).

Table 18: Seattle Angina Questionnaire Results from Published Reducer Studies

Study [Time Period]	Physical Limitations		Anginal Stability		Angina Frequency		Treatment Satisfaction		Quality of Life	
	Baseline	Follow-up	Baseline	Follow-up	Baseline	Follow-up	Baseline	Follow-up	Baseline	Follow-up
COSIRA Treatment Arm [6 months]	47.4 (24.7)	56.5 (27.1)	43.1 (22.4)	61.3 (27.5)	43.7 (25.9)	59.0 (29.3)	79.7 (18.6)	82.6 (17.6)	42.3 (19.7)	60.0 (23.7)*
Konigstein, EuroIntervention (2018a) [6 months]	42.8 (20.5)	57.6 (26.7)**	21.7 (21.7)	55.4 (35.3)***	36.5 (25.6)	68.7 (33.6)***	60.1 (20.0)	77.9 (23.2)**	23.2 (17.5)	47.1 (26.0)***
Giannini, JACC (2018b) [12 months]	47.9 (15.2)	63.4 (16.6)***	40.7 (11.5)	55.6 (19.0)***	45.0 (19.1)	66.1 (19.8)***	38.2 (14.9)	70.7 (14.5)***	26.0 (12.5)	58.3 (20.1)***
Gallone EHJ (2020) Median (IQR) [15 months]	47 (35–55)	57 (47–52)***	40 (25–43)	60 (40–80)***	50 (40–63)	61 (50–83)***	48 (34–73)	80 (70–82)***	29 (17–40)	62 (47–75)***
Giannini Int J Card (2018a) [14 months]	44.5 (18.6)	62.2 (20.7)***	37.1 (21.2)	66.6 (27.0)***	44.8 (22.4)	66.7 (20.8)***	51.9 (21.6)	68.4 (17.6)***	27.1 (16.9)	52.2 (19.9)***
D'Amico GISE (2019) [18 months]	44	63.2***	41.1	69.9***	45.7	70.7***	46	74.7***	32.5	63.3***
Ponticelli Int J Card (2019) [2 years]	47.9 (14.7)	67.1 (13.8)***	39.8 (12.0)	45.2 (14.0)	44.4 (19.2)	69.0 (15.1)***	37.9 (14.7)	74.0 (8.4)***	25.7 (12.4)	58.7 (18.1)***

Note: Data are shown as mean (SD) unless otherwise noted.
* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

The COSIRA secondary endpoint analysis of exercise duration did not have a pre-specified hypothesis test. This analysis showed a strong trend toward significance in total exercise duration, with a mean increase of 64.7 seconds in the Reducer group and 4.3 seconds in the Control group. The mean exercise duration in COSIRA was higher than that seen in 2 ranolazine studies used to gain FDA approval (CARISA and MARISA): the CARISA study showed a mean trough exercise duration of 24 seconds (Chaitman et al 2004a), and the MARISA study showed a mean difference of 23.8–45.9 seconds depending on the dose (Chaitman et al 2004b). The peak mean exercise duration was 29.3–55 seconds in the MARISA study and 26–34 seconds depending on the dose in the CARISA study.

The Konigstein reference states there was objective improvement in physical capacity (Table 19). The Giannini reference states the treadmill tests were available in 51 patients with no significant improvement observed, but it did note a significantly lower number of treadmill tests interrupted for limiting angina at peak stress.

Table 19: Supportive Clinical Testing ETT Total Exercise Duration

Study	Total Exercise Duration at Baseline	Total Exercise Duration at Follow-up (Time Period)
COSIRA Treatment Arm (seconds)	441.29 ± 193.74	449.81 ± 194.32 (6 months)
Konigstein (2018a) (minutes)	03:43 ± 01:30	04:35 ± 02:18 (6 months)
Giannini (2018a) (seconds)	375 ± 169	388 ± 224 (14 months)

Although the 6MWT was not assessed in the COSIRA study, published studies demonstrate a statistically significant increase in physical capacity and exercise tolerance (Table 20).

Table 20: Supportive Clinical Evidence 6MWT

Study	Total Exercise Duration at Baseline	Total Exercise Duration at Follow-up (Time Period)
Konigstein (2018a)	299.9 ± 97.9	352.9 ± 75.3 (6 months)
Giannini (2018a)	307.5 ± 129.0	386.9 ± 99.9 (14 months)

6 CLINICAL SAFETY

Summary

- The COSIRA study results, which demonstrated that the Reducer is safe in patients with refractory angina, are supported by published, peer-reviewed literature from multiple publications.
- The Reducer treatment arm had similar rates of AEs, severe AEs, SAEs, and MAEs compared with the Control arm. The majority of AEs were mild or moderate and were not related to the device or procedure.
- The majority of the SAEs reported were categorized as cardiac disorders, as would be expected for this patient population.
- Safety outcomes from COSIRA included 5 MAEs (1 Reducer, 4 Control). There was one MI in the Reducer group compared with 3 MIs and a cardiac death in the Control group.
- In the REDUCER-I postmarket study interim progress report, there was 1 unknown procedure- or device-related MACE up to 2 years follow-up, for an overall rate of 0.4%.
- Published literature reporting safety outcomes from a 12-year follow-up of FIM patients supports the durability and patency of the Reducer. There were no events of migration, deformation, occlusion, or thrombosis.
- Overall, the totality of available clinical evidence based on Neovasc-conducted studies, available literature, and postmarket findings of the Reducer System has demonstrated a very low incidence of device- and procedure-related complications and the absence of UADEs.

6.1 Safety Population

Neovasc has clinical study data available for approximately 300 patients with various follow-up periods up to 5 years in 3 clinical studies, including a double-blind, randomized, sham-controlled study (COSIRA). Neovasc has completed the FIM and COSIRA clinical studies, and currently has an active postmarket observational study (REDUCER-I) underway in Europe to collect long-term (5-year) safety and performance data on the use of the Reducer System. The focus of this safety presentation is on data from COSIRA. The safety population included all randomized patients and was evaluated according to the actual treatment received. Two patients who were randomized to the Reducer arm in COSIRA but did not receive the device were analyzed as control patients for safety.

6.2 Safety Findings in COSIRA

6.2.1 Adverse Events

Table 21 provides an overview of AEs in COSIRA. In this study, a similar percentage of patients in each study arm experienced AEs (64.0% in the Reducer arm and 69.5% in the Control arm). The majority of AEs in both arms were mild to moderate in severity, with 8.0% and 11.1% of patients in the Reducer and Control arms, respectively, experiencing severe AEs. More patients in the Control arm (20.4%) experienced SAEs than in the Reducer arm (12.0%). There was one death, which was in the Control arm and is detailed in Section 6.5. A full list of AEs by system organ class (SOC) is provided in Appendix 10.3.

Table 21: COSIRA: Summary of Adverse Events (Safety Population)

	COSIRA	
Patients with Events, n (% of patients)	**Reducer N Patients=50**	**Control N Patients=54**
Adverse Events	32 (64.0)	37 (68.5)
Mild	21 (42.0)	23 (42.6)
Moderate	18 (36.0)	21 (38.9)
Severe	4 (8.0)	6 (11.1)
Serious Adverse Events	6 (12.0)	11 (20.4)
Deaths	0	1 (1.9)

6.2.1.1 Adverse Events by Time

In COSIRA, in the time period prior to discharge, more AEs occurred in the Reducer arm (9.2%) than the Control arm (3.2%) (Table 22). In the period between discharge and 30-day follow-up, there were fewer AEs in the Reducer arm (21.1%) than in the Control arm (29.0%). After 30 days, the rates for AEs and SAEs were comparable in both arms.

Table 22: COSIRA: Summary of Adverse Events by Time (Safety Population)

Number of Events – n (% of total events)	Reducer N Total Events=76	Control N Total Events=93
Prior to Discharge		
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*		
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		
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		
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**		
Any adverse events	0 (0)	0 (0)
Serious adverse events	0 (0)	0 (0)
Deaths	0 (0)	0 (0)

* Note: One event was considered to have occurred prior to the 30-day follow-up by the investigator as the event happened when the patient was officially discharged; the patient had to be re-admitted by referral to the emergency room.
** Only the patients from one site (n=4) had a 12-month follow-up visit.

6.2.1.2 Adverse Events by Severity

As shown in Table 21, the majority of AEs in COSIRA were mild (42.0% Reducer and 42.6% Control) or moderate (36.0% Reducer and 38.9% Control). The severity of AEs was balanced between the study arms, with the exception that the Control arm had a greater proportion of severe events (8.0% Reducer, 11.1% Control).

6.2.2 Procedure-/Device-Related Adverse Events

In COSIRA, the majority of the AEs were judged to be not related to the procedure or the device (Table 23). Seven events were considered related or probably related to the procedure (5 Reducer, 2 Control). Events in the Reducer arm included puncture site bleeding, chest pain, unstable angina, arrhythmia, and gastrointestinal bleeding. Events in the Control arm included elevation of troponin and bleeding at puncture site.

Three of the procedure-related events (unstable angina, arrhythmia, and gastrointestinal bleeding) were also considered related or probably related to the device.

Table 23: COSIRA: Adverse Events Related to Procedure/Device (Safety Population)

Number of Events – n (%)	Reducer N Total Events=76 n (%)	Control N Total Events=93 n (%)
Relationship to Procedure		
Not related	68 (89.5)	88 (94.6)
Unlikely	3 (3.9)	3 (3.2)
Probably related*	2 (2.6)	0 (0)
Related	3 (3.9)	2 (2.2)
Relationship to Device		
Not related	69 (90.8)	92 (98.9)
Unlikely	4 (5.3)	1 (1.1)
Probably related*	1 (1.3)	0 (0)
Related	2 (2.6)	0 (0)

*Or "possibly related," according to the CEC.

6.2.3 Serious Adverse Events

In COSIRA, 6 (12.0%) patients in the Reducer arm and 11 (20.4%) patients in the Control arm experienced SAEs (Table 24). The majority of the SAEs were categorized as cardiac disorders, as would be expected for this patient population. 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).

There were 2 periprocedural (i.e., within 30 days post-procedure) SAEs that both occurred in the same patient with the Reducer: an MI shortly after discharge and again at 27 days post-procedure.

Table 24: COSIRA: Serious Adverse Events (Safety Population)

MedDRA System Organ Class Preferred Term	COSIRA Reducer N Patients=50 n (%)	COSIRA Control N Patients=54 n (%)
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)
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)

6.2.4 Technical Observations

A device deficiency was recorded any time that the originally opened Reducer was not used for implantation and a second Reducer had to be opened. A total of 9 device deficiencies occurred, the majority of which (8/9) were the result of operator mishandling (Table 25). In one case, the operator had to use a second device due to clots (not related to the Reducer System) that were noticed in the guide catheter and on the wire.

Table 25: COSIRA: Summary of Device Deficiencies (Safety Population)

Device Deficiencies	Reducer Arm (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 patients implanted with the Reducer, there was 1 device malfunction (2.0%). In this patient, the Reducer slipped on the balloon while advancing the undeployed

device to the intended location for implantation. The malfunction was not noticed by the physician until the device was inflated and deployed. At that point, it was apparent that the device would not perform as intended as the device was deployed without the central narrowing. A peripheral angioplasty balloon was inserted and expanded the mal-deployed Reducer. The physician elected to proceed and successfully deployed a second Reducer within the mal-deployed Reducer, and the patient left the cardiac catheterization laboratory with no sequelae.

Following this event, at subsequent implantations at all sites, the implanting physician was advised to verify that the Reducer was between the marker bands prior to exiting the guide catheter, as stated in the Instructions for Use. If the Reducer was not located between the marker bands, the entire device was to be removed as a single unit under direct fluoroscopy visualization and the implantation re-attempted with a new device.

6.3 Safety Findings in REDUCER-I

The design of REDUCER-I is discussed in Section 5.2.1. The primary safety endpoints in REDUCER-I were the rate of occurrence of device- and/or procedure-related SAEs and the rate of MACE, which is described in Section 6.4.

In REDUCER-I, 98 patients (40.7%) reported AEs throughout the follow-up period of up to 5 years. A total of 59 (24.5%) patients experienced SAEs, of which 8 (3.3%) were procedure-related and 3 (1.2%) were device-related. Thirteen deaths were reported, 10 of which were adjudicated by the CEC as unrelated to the device and/or the procedure. At the time of the Premarket Application submission, 3 events were pending adjudication; since that time, 2 events were adjudicated as not related to device or procedure, and 1 event has not yet been adjudicated as of 03 August 2020. These data have not been reviewed by FDA. There have been no UADEs reported in REDUCER-I.

Table 26 provides an overview of the Endpoint-Related adverse events in REDUCER-I. The most frequently occurring event was Angina as an Adverse Event (n=66) occurring in 18.7% of the enrolled patients. Of these angina events, only 1 (0.4%) was adjudicated as being related to the procedure and device. MI was the second most frequently reported (n=21), occurring in 6.6% of patients (N=16). Of these MI events, only 1 (0.4%) was adjudicated as being related to the procedure and device. There have been no UADEs reported in REDUCER-I.

Table 26: REDUCER-I Endpoint-Related Adverse Events

Event	Events n/N (%)	Patients n/N (%)	Procedure-Related Patients n/N (%)	Device-Related Patients n/N (%)	*SAE Events n/N (%)*	*SAE Patients n/N (%)*	*SAE Procedure-Related Patients n/N (%)*	*SAE Device-Related Patients n/N (%)*
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.

6.4 Cardiovascular Safety

Major Adverse Events in COSIRA

MAEs were defined as a composite of cardiac death, major stroke, and MI through hospital discharge and at 30-day, 3-month, and 6-month post-procedural evaluations.

A total of 5 MAEs were reported, as adjudicated by the CEC. There was 1 MI in the Reducer arm and 3 MIs and a cardiac death in the Control arm (Table 27). The incidence of MAEs was lower in the Reducer arm (2.0%) than in the Control arm (7.7%). None of the 5 events occurring after 30 days post-procedure were attributed to the procedure or investigational device. One MI was considered by the CEC to be related to a study-specific assessment, as it occurred during the study-required dobutamine stress ECHO at the 6-month follow-up.

Table 27: COSIRA: Major Adverse Events Occurring after 30 Days Post-Procedure

Adverse Event – n (%)	Reducer N Patients=50	Control N Patients=54
Any Major Adverse Event	1 (2.0)	4 (7.7)
Cardiac death	0 (0)	1 (1.9)
Major stroke	0 (0)	0 (0)
Myocardial infarction	1 (2.0)	3 (5.6)

Major Adverse Cardiovascular Events in REDUCER-I

MACE is a composite of cardiac death, major stroke, and MI post-implant. There were 32 adjudicated MACE events in 23 patients in REDUCER-I (Table 28). One event was adjudicated as unknown if device- and/or procedure-related, as the CEC did not have the documentation available to definitively determine the relationship to the device and/or procedure.

Table 28: MACE Events in REDUCER-I

	Events n/N (%)	Patients n/N (%)	Procedure-Related Patients n/N (%)	Device-Related Patients n/N (%)
Cardiac death	6/32 (18.8%)	6/228 (2.6%)	0	0
Major stroke	5/32 (15.6%)	4/228 (1.8%)	0	0
Myocardial infarction	21/32 (65.6%)	16/228 (7.0%)	1/228 (0.4%)	1/228 (0.4%)
Total	**32**	**23/228 (10.1%)**	**1/228 (0.4%)[1]**	**1/228 (0.4%)[1]**

Note: MACE events leading to a cardiac death are counted as Cardiac Death and not the event that led to the death.

[1] 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 definitively determine the relationship to the device and/or procedure.

6.5 Deaths

In COSIRA, 1 death occurred in a patient in the Control arm who died of multi-organ failure on Day 118. The death was adjudicated by the CEC as not related to the procedure or the device.

The patient was randomized to the Control group in COSIRA on 10 October 2012. On 16 December 2012, the patient was hospitalized for pulmonary edema, which was not related to the procedure, and then discharged from the hospital 3 days later (19 December 2012). The patient presented on 1 January 2013 with pneumonia (not related to the procedure) and was not hospitalized for this condition. On 16 January 2013, the patient was admitted to the hospital for unstable angina (not related to the procedure), underwent PCI to the left anterior descending, and was discharged from the hospital on 17 January 2013. The patient was re-admitted on 20 January 2013 with unspecified life-threatening arrhythmia (not related to the procedure) which required medication, cardiopulmonary resuscitation and a temporary pacemaker. The patient succumbed to multisystem failure on 5 February 2013. All events were adjudicated by the CEC and none were found to be related to the procedure. The CEC considered both events (arrhythmia and multisystem failure) as one event.

In REDUCER-I, 13 deaths were reported, 10 of which were adjudicated by the CEC as unrelated to the device and/or the procedure. At the time of the PMA submission, 3 events were pending adjudication; since that time, 2 events were adjudicated as not related to device or procedure, and 1 event has not yet been adjudicated as of 3 August 2020 but was reported as not related to the device or the procedure by the investigator. These data have not been reviewed by FDA.

6.6 Postmarket Safety Data

The Postmarket Surveillance data demonstrated that there were no new events identified that had not previously been considered in the risk management documentation. Overall, the rate of ADEs was low across studies (Table 29). The Reducer System continues in commercial release to demonstrate an acceptable safety profile.

Table 29: Reducer System Adverse Device Effects

	FIM N=15		COSIRA N=52		REDUCER-I[1] N=204		Commercial Use N=1840		SAE
Potential Harm	**Count**	**Rate**	**Count**	**Rate**	**Count**	**Rate**	**Count**	**Rate**	**Count**
Access site complications	0	0.00%	**1**	**1.92%**	**13**	**6.37%**	0	0.00%	**3**
Arrhythmias (e.g. ventricular tachycardia or ventricular fibrillation)	0	0.00%	**1**	**1.92%**	**4**	**1.96%**	0	0.00%	**1**
Angina	0	0.00%	0	0.00%	**3**	**1.47%**	0	0.00%	**2**
Minor neurological event, including dysphasia, blurred vision, or TIA	0	0.00%	0	0.00%	**3**	**1.47%**	0	0.00%	0
Dissection (e.g. coronary sinus)	0	0.00%	0	0.00%	**4**	**1.96%**	**2**	**0.11%**	**1**
Reducer malposition, migration or embolization	**1**	**6.67%**	**2**	**3.85%**	**2**	**0.98%**	**10**	**0.54%**	**4**
Chest Pain	0	0.00%	**1**	**1.92%**	**1**	**0.49%**	0	0.00%	0
Minor or Major bleeding event (e.g. hemorrhage, cardiac tamponade or pericardial effusion)	0	0.00%	**1**	**1.92%**	**1**	**0.49%**	**1**	**0.05%**	**3**
Ischemic events (e.g. myocardial infarction, or unstable angina)	0	0.00%	**1**	**1.92%**	0	0.00%	0	0.00%	**1**
Perforation of coronary sinus	0	0.00%	0	0.00%	**1**	**0.49%**	**3**	**0.16%**	**3**
Hypotension/hypertension	0	0.00%	0	0.00%	0	0.00%	**1**	**0.05%**	**1**
Allergic reaction	0	0.00%	0	0.00%	0	0.00%	0	0.00%	0
Embolism (e.g. pulmonary or vessel)	0	0.00%	0	0.00%	0	0.00%	0	0.00%	0
Conduction Disturbances	0	0.00%	0	0.00%	0	0.00%	0	0.00%	0
Infection	0	0.00%	0	0.00%	0	0.00%	0	0.00%	0
Vascular event (e.g. pseudoaneurysm or thrombus)	0	0.00%	0	0.00%	0	0.00%	0	0.00%	0
Pulmonary edema	0	0.00%	0	0.00%	0	0.00%	0	0.00%	0
Reducer and/or coronary sinus occlusion (e.g. thrombosis	0	0.00%	0	0.00%	0	0.00%	0	0.00%	0
Reducer fracture	0	0.00%	0	0.00%	0	0.00%	0	0.00%	0
Respiratory failure	0	0.00%	0	0.00%	0	0.00%	0	0.00%	0
Spasm of CS or jugular vein	0	0.00%	0	0.00%	0	0.00%	0	0.00%	0
Cardiac valve injury (tricuspid)	0	0.00%	0	0.00%	0	0.00%	0	0.00%	0
Myocardial damage	0	0.00%	0	0.00%	0	0.00%	0	0.00%	0
Pyrogenic, immunological or toxicological reaction	0	0.00%	0	0.00%	0	0.00%	0	0.00%	0

[1] Data cutoff is 12 Aug 2019 and included non-adjudicated and adjudicated adverse events.
Note: Adverse events of Commercial Use comprise events reported to Neovasc and handled within the Complaint Handling System under 21 CFR 820.198.

6.7 Long-Term Safety in Published Literature

Long-Term Safety

The long-term safety of the Reducer is supported by published results from an Investigator-initiated study that evaluated patients from the FIM Study (Parikh et al 2018). This 12-year follow-up was conducted at a single center in India that had participated in the Reducer System FIM Study and included CT angiography imaging to evaluate the location of the Reducer within the CS, and to rule out migration and occlusion of the Reducer. The primary outcome at 12 years was confirmation of the position, integrity, and patency of the Reducers by CT angiography. Follow-up CT angiography results were analyzed both by the medical center and by an independent core laboratory and were compared with CT angiography performed 6 months post-Reducer implantation. Secondary outcomes were improvement in angina class (Section 5.2.2) and prevalence of MACE.

Of the 10 patients treated with Reducer at the site, 7 were available for follow-up at 12 years. All Reducers were positioned properly in the proximal segment of the CS, with no migration, occlusion, or thrombosis. The mean diameters of the Reducers were comparable to the diameters measured at 6 months. Additionally, no strut fractures, deformity, or distortions were detected, with appropriate blood flow through all Reducers. One device demonstrated hypoattenuation (defined as intimal proliferation), consistent with what is typically seen in coronary artery stents.

Of the 10 patients who underwent Reducer implantation at this site, 3 experienced MACE: 1 patient underwent CABG at 18 months and was still alive at the data cutoff date, while 2 patients died due to cardiac causes at 11 years. One patient was alive and clinically well at the data cutoff date but did not participate in the 12-year follow-up.

In this small group of patients, long-term structural, anatomical, and clinical follow-up demonstrates the durability and patency of the Reducer.

Additional Published Literature

Major AEs and major procedure-related AEs have been reported in the literature with the Reducer. The rates of these events have been relatively low (Table 30), supporting the safety of the Reducer implantation.

Table 30: Supportive Clinical Evidence MACE

Study	Cardiac Death	Major Stroke	Myocardial Infarction	Major Procedure-Related AE
	Number of Patients (%)			
COSIRA Treatment Arm (6 months)	0 (0)	0 (0)	1 (2.0)	1 (2.0)
COSIRA Control Arm (6 months)	1 (1.9)	0 (0)	3 (5.6)	0 (0)
Konigstein, 2018a (6 months)	None Reported	0 (0)	0 (0)	0 (0)
Giannini, 2018 (12 Months)	0 (0)	1 (2)	1 (2)	0 (0)
Gallone, 2019 (15 months)	10 (4.7)	None Reported	15 (7.1)	0 (0)
Giannini, 2018 (14 months)	4 (2.8)	None Reported	2 (1.4)	0 (0)
D'Amico, 2019 (564 days)	7 (3.8)	None Reported	13 (7.1)	8 (4.3)*
Ponticelli, 2019 (2 years)	1 (2.4)	1 (2.4)	3 (7.1)	0 (0)

* Presentation did not specify whether these events were minor or major so all were included.

7 PROPOSED POSTMARKET RANDOMIZED CONTROLLED TRIAL

To further confirm the safety and effectiveness of the Reducer System for treatment of patients with refractory angina, Neovasc has proposed a postmarket multi-center, randomized, double-blind, sham-controlled study, REDUCER-II. The design of REDUCER-II is based on COSIRA-II, which was submitted as part of the approved IDE. A minimum of 236 participants at up to 25 investigational centers in North America, which is proposed to include multiple centers in Canada where the device is not currently approved. Participants will be randomized and followed at baseline, procedure, discharge, 30 days, 90 days, 6 months, 1 year and annually through 5 years. The primary endpoint is the responder rate, defined as increase of ≥ 60 seconds in exercise duration in modified Bruce treadmill exercise tolerance testing at 6 months post-procedure compared to baseline.

The planned sample size is based on a 1:1 randomization allocation, assumed responder rates of 27.5% and 50% for the control and treatment groups respectively, a one-sided 0.025 alpha level for an exact binomial test, and a desire for greater than 90% power accounting for attrition of up to 10%. An interim analysis, employing a “promising zone approach” (Mehta and Pocock 2011) will be used to potentially adjust the sample size to ensure adequate power, up to a maximum of 500 subjects.

Steps will be taken to enroll women and underrepresented populations in the study. If requested by the participant, he or she may be unblinded to the treatment assignment after completion of the 6-month follow-up visit. Participants randomized to the Control arm will be allowed, but not required, to cross over to the treatment arm at the 6-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. Study Investigators will be trained on the use of the Reducer System. Implanting investigators will be required to complete device training prior to first implant, and only trained investigators will be allowed to treat participants in the trial.

8 BENEFIT-RISK CONCLUSIONS

The Reducer System Fulfills a Significant Unmet Need for “No Option” Patients

Refractory angina pectoris severely impacts patients’ quality of life, leaving them with pain and disability. Despite advances in new drug and device therapies for treating CAD, many patients with refractory angina remain severely disabled by the condition. These “no option” patients currently have limited treatment options and are in need of additional treatments to improve their quality of life.

The FDA has recognized this unmet need by granting the Reducer System Breakthrough Device Designation. In order to facilitate earlier patient access to Breakthrough devices that demonstrate the potential to address an unmet medical need, FDA may accept a higher degree of uncertainty about the benefit-risk profile of the device at the time of approval by collecting certain data in the postmarket setting rather than premarket.

As discussed above, current treatment options for refractory angina are exhausted with less than optimal results, indicating that there is still an unmet need in a well-defined patient population, and novel therapeutic options for this group of patients would be welcomed by physicians and in the best interest of these “no option” patients.

COSIRA Met its Effectiveness Endpoint, with Consistent Supportive Evidence in REDUCER-I

The effectiveness findings from clinical studies with the Reducer demonstrate that the Reducer improves life-altering symptoms in patients with refractory angina. The double-blind, randomized, sham-controlled study, COSIRA, met its primary endpoint, as significantly more patients in the Reducer group than the Control group achieved a ≥ 2 CCS class improvement at 6 months. Similarly, more patients in the Reducer group than the Control group achieved a ≥ 1 CCS class improvement at 6 months. SAQ Quality of Life scores also showed statistical significance favoring the Reducer group over the Control group (secondary endpoint analyses were not pre-specified and did not account for multiplicity). Results from dobutamine stress ECHO and ETT also showed directional consistency in favor of the Reducer arm. CT angiography at 6 months confirmed there were no device migrations and all devices were patent.

Data from the REDUCER-I interim report provide supportive effectiveness evidence for up to 5 years of follow-up (n=22). Improvement in ≥ 1 CCS class was observed in the majority of patients, and ≥ 2 CCS classes in approximately one-third of patients at 2 years and this improvement was maintained out to 5 years. The Reducer also improved scores on the SAQ domains of Physical Limitations, Anginal Stability, and Anginal Frequency, and increased 6MWT and total exercise duration on the ETT at 1 year. Similar results have been reported in multiple publications from sites that have participated in various postmarket clinical studies/registries across multiple

geographies, further providing assurance of safety and effectiveness as observed in COSIRA.

According to the regulations (21 CFR 860.7(e)(1)), there is reasonable assurance that a device is effective when it can be determined, based upon valid scientific evidence, that in a significant portion of the target population, the use of the device for its intended uses and conditions of use, when accompanied by adequate directions for use and warnings against unsafe use, will provide clinically significant results. The Reducer has met this threshold with the data provided in COSIRA, supported by the data from REDUCER-I as well as the multiple publications of real-world evidence.

Totality of Evidence Demonstrates Safety of Reducer

The risks of the Reducer have been established in a randomized, double-blind, sham-controlled, multi-center study, COSIRA, and an ongoing postmarket observational study, REDUCER-I. Importantly, 12 years after implantation of the Reducer in the FIM Study, no migration, occlusion, or deformation were observed with CT angiography in a subset of 7 patients, with a sustained improvement in angina class. The COSIRA trial confirmed the Reducer demonstrated excellent technical and procedural success. The Reducer treatment arm had similar rates of AEs, severe AEs, SAEs, and MAEs compared with the Control arm. There was 1 MI in the Reducer group and 3 MIs and a cardiac death in the Control arm.

A report from the ongoing REDUCER-I postmarket study supports the safety findings in COSIRA. There were no UADEs and no deaths adjudicated as procedure- or device-related. Additional publications have shown consistent results for MACE with the Reducer, supporting its safety.

According to the regulations (21 CFR 860.7(d)(1)), there is reasonable assurance that a device is safe when it can be determined, based upon valid scientific evidence, that the probable benefits to health from use of the device for its intended uses and conditions of use, when accompanied by adequate directions and warnings against unsafe use, outweigh any probable risks. The Reducer has met this threshold with the data provided in COSIRA, supported by the data from REDUCER-I as well as the multiple publications of real-world evidence.

Positive Benefit-Risk Profile of the Reducer System

The Reducer System fulfills a significant unmet need as a treatment option for “no option” patients with refractory angina. Results from clinical trials and real-world experience provide strong evidence that the Reducer is both safe and effective in providing symptom relief and improving quality of life for patients who have failed other therapies and still suffer from the disabling condition of refractory angina pectoris. Consistent with FDA published initiatives to provide timely access to safe and effective medical devices to patients with unmet needs, greater reliance on postmarket data collection may be considered to address any uncertainty in the premarket data.

Accordingly, Neovasc has proposed a robust randomized, double-blind, sham-controlled postmarket study to provide further evidence of the safety and effectiveness of the Reducer System.

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10 APPENDICES

10.1 COSIRA Inclusion and Exclusion Criteria

Inclusion Criteria

1. Patient is older than 18 years of age
2. Symptomatic CAD with chronic refractory angina pectoris classified as CCS 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 (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

Angiographic Exclusion Criteria

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 superior vena cava); and/or
- CS diameter at the site of planned reducer implantation less than 9.5 mm or greater than 13 mm

Clinical & General Exclusion Criteria

1. Recent (within 3 months) acute coronary syndrome
2. Recent (within 6 months) successful PCI or CABG
3. Unstable angina (recent onset angina, crescendo angina, or rest angina with ECG changes) during the 30 days prior to screening

4. De-compensated CHF or hospitalization due to CHF during the 3 months prior to screening
5. Life-threatening rhythm disorders or any rhythm disorders that would require placement of an internal defibrillator and/or pacemaker
6. Severe COPD as indicated by a forced expiratory volume in one second that is less than 55% of the predicted value
7. Patient cannot undergo ETT (bicycle) for reasons other than refractory angina
8. Severe valvular heart disease
9. Patient with pacemaker or defibrillator electrode in the right atrium, right ventricle, or CS
10. Patient having undergone tricuspid valve replacement or repair
11. Chronic renal failure (serum creatinine > 2 mg/dL), including patients on chronic hemodialysis
12. Moribund patients, or patients with comorbidities limiting life expectancy to less than one year
13. Contraindication to required study medications that cannot be adequately controlled with pre-medication
14. Known allergy to stainless steel or nickel
15. Contraindication to having an MRI performed (cardiac MRI subset patients only)
16. 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

10.2 Effectiveness Measures

10.2.1 Dobutamine ECHO Wall Motion Score Index

The dobutamine ECHO 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 being given a score of 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, as the Reducer is placed in the CS distal to where the right coronary artery drains, a modified LCA WMSI was calculated as described above using only the 11 segments attributed to the LCA system (Basal and Mid – anteroseptum, anterior, anterolateral, inferoseptum; Apical – septal, anterior, lateral). WMSI and modified LCA WMSI were calculated on both resting and stress testing.

10.2.2 Exercise Stress Test

A bicycle ergometry stress test was adapted from the Asymptomatic Cardiac Ischemia Pilot protocol. 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 do so.
- Time to 1 mm ST segment duration: the time that the patient exercised until exhibiting ST segment depression of 1 mm or greater.
- Maximal ST segment depression: the total measurement of ST segment depression exhibited by the patient while undergoing exercise testing.
- Metabolic equivalent to tasks: 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.

10.3 Adverse Events by System Organ Class in COSIRA

Table 31: COSIRA: All Adverse Events by System Organ Class (Safety Population)

MedDRA System Organ Class – n (%) Preferred Term	Reducer N=50	Control N=54
Any Adverse Event	**32 (64.0)**	**37 (68.5)**
Blood and Lymphatic System Disorders	**2 (4.0)**	**4 (7.4)**
Anemia	2 (4.0)	3 (5.6)
Lymphadenopathy	0 (0)	1 (1.9)
Cardiac disorders	**15 (30.0)**	**16 (29.6)**
Acute coronary syndrome	0 (0)	2 (3.7)
Acute myocardial infarction	1 (2.0)	0 (0)
Angina pectoris	9 (18.0)	11 (20.4)
Angina unstable	1 (2.0)	5 (9.3)
Arrhythmia	3 (6.0)	1 (1.9)
Atrioventricular block	0 (0)	1 (1.9)
Bradyarrhythmia	2 (4.0)	0 (0)
Cardiac failure chronic	2 (4.0)	1 (1.9)
Myocardial infarction	1 (2.0)	1 (1.9)
Pericarditis	0 (0)	1 (1.9)
Tachyarrhythmia	1 (2.0)	0 (0)
Eye disorders	**2 (4.0)**	**1 (1.9)**
Cataract	1 (2.0)	0 (0)
Vision blurred	0 (0)	1 (1.9)
Visual impairment	1 (2.0)	0 (0)
Gastrointestinal disorders	**3 (6.0)**	**3 (5.6)**
Abdominal pain upper	0 (0)	1 (1.9)

MedDRA System Organ Class – n (%) Preferred Term	Reducer N=50	Control N=54
Crohn's disease	1 (2.0)	0 (0)
Gastritis	0 (0)	1 (1.9)
Gastrointestinal hemorrhage	1 (2.0)	0 (0)
Esophageal spasm	1 (2.0)	0 (0)
Paresthesia oral	1 (2.0)	0 (0)
Vomiting	0 (0)	1 (1.9)
General disorders and administration site conditions	**11 (22.0)**	**10 (18.5)**
Chest pain	4 (8.0)	3 (5.6)
Exercise tolerance decreased	1 (2.0)	0 (0)
Fatigue	5 (10.0)	3 (5.6)
Multi-organ failure	0 (0)	1 (1.9)
Edema	0 (0)	2 (3.7)
Puncture site hemorrhage	1 (2.0)	2 (3.7)
Puncture site pain	1 (2.0)	0 (0)
Pyrexia	1 (2.0)	0 (0)
Hepatobiliary disorders	**0 (0)**	**1 (1.9)**
Hepatomegaly	0 (0)	1 (1.9)
Infections and infestations	**3 (6.0)**	**3 (5.6)**
Infection	1 (2.0)	0 (0)
Localized infection	0 (0)	1 (1.9)
Pneumonia	2 (4.0)	1 (1.9)
Urinary tract infection	0 (0)	1 (1.9)
Injury, poisoning and procedural complications	**2 (4.0)**	**0 (0)**
Laceration	1 (2.0)	0 (0)
Limb injury	1 (2.0)	0 (0)
Investigations	**0 (0)**	**3 (5.6)**
Blood urine present	0 (0)	1 (1.9)
Weight increased	0 (0)	1 (1.9)
Troponin increased	0 (0)	1 (1.9)
Metabolism and nutrition disorders	**1 (2.0)**	**0 (0)**
Hyperkalemia	1 (2.0)	0 (0)
Musculoskeletal and connective tissue disorder	**2 (4.0)**	**5 (9.2)**
Arthralgia	1 (2.0)	1 (1.9)
Muscle spasms	1 (2.0)	0 (0)
Musculoskeletal pain	0 (0)	1 (1.9)
Neck pain	0 (0)	1 (1.9)
Pain in extremity	0 (0)	3 (5.6)
Nervous system disorder	**5 (10.0)**	**1 (1.9)**
Peripheral nerve injury	1 (2.0)	0 (0)
Amnesia	1 (2.0)	0 (0)
Dizziness	2 (4.0)	0 (0)
Headache	0 (0)	1 (1.9)
Memory impairment	1 (2.0)	0 (0)
Psychiatric disorders	**1 (2.0)**	**2 (3.7)**
Depression	1 (2.0)	2 (3.7)
Insomnia	0 (0)	1 (1.9)
Reproductive system and breast disorders	**1 (2.0)**	**2 (3.7)**
Benign prostatic hyperplasia	1 (2.0)	0 (0)
Erectile dysfunction	0 (0)	1 (1.9)
Peyronie's disease	0 (0)	1 (1.9)

MedDRA System Organ Class – n (%) Preferred Term	Reducer N=50	Control N=54
Respiratory, thoracic and mediastinal disorders	**11 (22.0)**	**9 (16.7)**
Apnea	1 (2.0)	0 (0)
Chronic obstructive pulmonary disease	1 (2.0)	1 (1.9)
Cough	2 (4.0)	1 (1.9)
Dyspnea	6 (12.0)	4 (7.4)
Epistaxis	0 (0)	2 (3.7)
Oropharyngeal pain	1 (2.0)	0 (0)
Pulmonary edema	0 (0)	1 (1.9)
Respiratory disorder	0 (0)	1 (1.9)
Skin and subcutaneous tissue disorders	**0 (0)**	**1 (1.9)**
Rash	0 (0)	1 (1.9)
Surgical and medical procedures	**2 (4.0)**	**1 (1.9)**
Cataract operation	1 (2.0)	1 (1.9)
Corneal implant	1 (2.0)	0 (0)
Intraocular lens implant	0 (0)	1 (1.9)
Vascular disorders	**2 (4.0)**	**4 (7.4)**
Hypertension	1 (2.0)	2 (3.7)
Hypotension	1 (2.0)	2 (3.7)