SUMMARY OF SAFETY AND EFFECTIVENESS (SSED)

I. GENERAL INFORMATION

Common name: Internal Vessel Occluder

Proprietary name: LeGoo®

Applicant's Name and Address: Pluromed, Inc.
175-F New Boston Street
Woburn, MA 01801

Date of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P110003

Date of FDA Notice of Approval: September 28, 2011

Expedited: Not applicable

II. INDICATIONS FOR USE

LeGoo® is indicated for temporary endovascular occlusion of blood vessels below the neck up to 4 mm in diameter.

III. CONTRAINDICATIONS

- Do not use LeGoo in patients with vascular anatomy or blood flow that precludes cannula placement or proper injection and control of LeGoo.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the Legoo labeling.

V. DEVICE DESCRIPTION

LeGoo is comprised of a 20% (weight percent in saline) of purified poloxamer 407, a non-toxic gel which is part of a family of biocompatible, water-soluble polymers that possess reverse, thermosensitive properties (i.e. as temperature increases, viscosity increases). Poloxamer 407 dissolves in blood and is excreted in urine.

At room temperature it is a viscous but injectable liquid, and it transitions to a temporary self-forming polymeric plug at body temperature. Because the material undergoes a temperature-induced phase change with no alteration in the product's chemical composition, the material does not "cure" *in situ*.

Principles of Operation

LeGoo is injected into a blood vessel that is intended to be occluded. The amount of LeGoo injected into the vessel is determined in relationship to the vessel diameter. An arteriotomy is made at a desired location, the cannula is inserted proximally, and LeGoo is injected against blood flow.

When LeGoo is injected into the blood vessel, the viscosity increases due to the increase in temperature and a plug is formed that occupies space in the vessel, temporarily preventing blood flow. LeGoo may also be injected distally to stop back bleeding. If left in place and not removed, the plug will dissolve in approximately 15 minutes, or blood flow may be restored by cooling the area with sterile ice or injecting cold saline.

LeGoo is supplied in a sterile single use syringe with three cannulas.

Table 1. LeGoo syringes

Product Code	*Product Description*
10-0025	LeGoo 0.25 mL
10-0050	LeGoo 0.5 mL
10-0100	LeGoo 1.0 mL
10-0250	LeGoo 2.5 mL

Table 2. Cannula

Product Code	*Product Description*
15-1040	Cannula 1.0 mm tip, 40 mm usable length
15-1540	Cannula 1.5 mm tip, 40 mm usable length
15-1580	Cannula 1.5 mm tip, 80 mm usable length
15-3080	Cannula 3.0 mm tip, 80 mm usable length

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are two broad categories of vascular occlusion devices available to surgeons to control bleeding:

1. Extravascular occlusion devices
2. Intravascular occlusion devices

The mode of action of extravascular occlusive devices is external pressure around the blood vessel. These devices include traditional surgical clamps, clips, vascular (vessel) loops and tapes. The mode of action of intravascular occlusive devices is temporary occlusion of blood flow within a target vessel. Each alternative has its own advantages and disadvantages.

VII. MARKETING HISTORY

LeGoo received a CE mark in 2007 and has been marketed by Pluromed in the European Union and a few other countries for the past 2 years. LeGoo has been marketed in the following countries Austria, Israel, Belarus, Italy, Belgium, Latvia, Bosnia-Herzegovina, Macedonia, Croatia, Netherlands, Czech Republic, Saudi Arabia, Denmark Singapore, Finland, Slovakia, France, Slovenia, Germany, Spain, Greece, Sweden, Hong Kong, Macau, Switzerland, Hungary, Turkey, Ireland, and United Kingdom. LeGoo has not been withdrawn from marketing for any reason related to the safety or effectiveness of the device.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Potential complications may include, but may not be limited to:

- Effects of transient occlusion of a blood vessel (e.g. infarction, undesired ischemia).
- Risks associated with the general procedure of clamping a blood vessel (e.g. fibrillation).
- Risks associated with cannulation (e.g. intimal wall injury.)
- Risks associated with application of LeGoo to epicardial or pericardial surfaces (e.g. adhesions)

For the specfic adverse events that occurred in the clinical study please see Section X below.

IX. SUMMARY OF PRECLINICAL STUDIES

A. Laboratory Studies

LeGoo is comprised of Poloxamer 407, (also known as Pluronic F127). The conformation of the polymer changes at a certain temperature, the "lower critical solubility temperature" (LCST), or also the "transition temperature." This

conformational change to the somewhat linear polymer allows it to form micelles, which cause an increase in viscosity. If the material is cooled below the transition temperature, then the conformation of the polymer changes back to a somewhat non- linear arrangement and the micelle falls apart. Also, micelles cannot form below a concentration of 12.5%. Once LeGoo is diluted in blood, the gel plug can no longer occlude the vessel. A table of the in vitro tests is included below.

Table 3. In vitro tests

In vitro test	*Results*	*Results*	*Acceptance Criteria*	*Test Purpose*
Viscosity	986 (cP)	Acceptable internal resistance to flow	≥ 700,000 cP	Verify the viscosity of the gel.
Transition temperature	17 °C	Acceptable transition from liquid to gel phase	16.2 – 19.2 °C	Verify proper purification of polymer and ensure that the correct polymer is chosen for final formulation.
Particulates	≥ 10 µm: 5535 ≥ 25 µm: 72	Meets USP criteria for IV injection, small volume	Light Obscuration >10 µm: 6000 max. >25 µm: 600 max. or Microscopic method >10 µm: 3000 max. >25 µm: 300 max.	Verify that material to be injected into the blood stream is within the USP criteria for particulates.
Endotoxins	< 1.2 EU/device	Meets the USP criteria for bacterial endotoxins	< 20 EU/device	Verify that the device is non-pyrogenic.
Bioburden	21 CFU	Meets internal criteria maintaining an SAL 10^{-6}	For product: Alert: 89 CFU Action: 146 CFU For verification testing: No growth in sterility test	Verify that the level of biological contamination is low enough to achieve a Sterility Assurance Level (SAL) of 10^{-6}.
In-vitro dissolution	658 sec	Sufficient dissolution to adequately allow for anastomosis and resume blood flow	N/A (this test is performed as a comparison for development purposes)	Measure the dissolution characteristics of the gel.

Biocompatibility/Toxicology

Biocompatibility testing of LeGoo and the cannulae for administration were performed as indicated in the FDA blue book memorandum #G95-1, "Use of International Standard ISO-10993, Biological Evaluation of Medical Devices Part 1: Evaluation and Testing, dated May 1, 1995. Both devices (LeGoo and the cannulae) are categorized as externally communicating devices with limited contact duration (less than 24 hours). As such, the following tests were performed:

Table 4. Summary of Biocompatibility Tests - LeGoo

Test	***Result***
Cytotoxicity (agar diffusion)	Non-cytotoxic
Sensitization	Non- sensitizing
Irritation (intracutaneous injection)	Non irritating
Systemic toxicity	Non-toxic
In-vitro hemocompatibility	Hemocompatible
Unactivated partial thromboplastin time	Not an activator of coagulation
Prothrombin time	No adverse effect on coagulation time
Complement activation	Did not induce complement activation
Hemolysis	Non-hemolytic

The cannula is inserted into the vessel and has limited contact duration with circulating blood of 5 to 10 seconds. The appropriate biocompatibility tests for the cannula are listed in the table below.

Table 5. Summary of Biocompatibility Tests – Cannula

Test	***Result***
Cytotoxicity (L929 Agar Diffusion)	Not cytotoxic
Sensitization (Kligman Maximization; Direct Contact)	Non-sensitizing
Irritation (Intracutaneous Injection)	Non-irritating
Systemic Injection	Non-toxic
Hemocompatibility	Hemocompatible

Sterilization

E Beam sterilization is used on LeGoo. All test methodologies and procedures and procedures are executed in accordance with AAMI, ISO, ASTM, and FDA requirements.

Packaging and Shelf-life

LeGoo is packaged in a foil pouch with an oxygen scavenger to prevent degradation via oxidation. This configuration has been tested for stability (ASTM F1980-02 Accelerated Aging for Medical Packaging) using accelerated aging and found to be stable for 2 years.

B. Animal Studies

The animal studies have assessed multiple vessel types including the coronary arteries, and have included multiple occlusions of the vessel. Occlusion time and the quality of occlusion have been measured. Varying concentrations of LeGoo and various product temperatures have been studied to determine the optimal concentration and temperature for vascular use. The time to spontaneous dissolution of the plug as well as the use of ice has been studied. Demonstration of complete dissolution and recanalization has been documented. Studies of the effect of LeGoo on arterial endothelium, microvascular reactivity, left ventricular function, and hyperemic response after reopening have been conducted. Blood samples have had routine hematology and chemistry analyses performed, as well as specific markers of myocardial, kidney or renal damage. General morphology of the liver and kidney were observed. Histopathology has been conducted (heart, liver and kidney), and animals assessed post-surgically for myocardial infarct.

Animal studies have demonstrated that poloxamer 407 does not cause abnormalities in coronary flow during reperfusion, and has no effect on endothelium independent microvessel relaxation. The porcine model has demonstrated preservation of endothelial function, lack of ischemic or infarction complications distally to bypassed arteries, and normal histology at the occlusion site and in distal myocardium. Temporary occlusion as a measure of effectiveness and reopening of the occluded vessel has also been demonstrated. Animal studies were inconclusive regarding regional myocardial function due to confounding by anesthesia and other experimental variables.

Summary of Animal Studies

Six preclinical swine studies were submitted in support of LeGoo. Two studies related to product development and four were either GLP or non-GLP safety and effectiveness studies in which swine were utilized in clinically-relevant operative scenarios. Mortality was strongly associated with ventricular fibrillation which was often difficult to conclusively associate to the test article or to the inherent technical difficulties of swine procedures. The following information summarizes the design and outcome of each of the preclinical studies. The following information summarizes the design and outcome of each of the preclinical studies.

Study # 1: A non-GLP feasibility study of acute effectiveness and safety in anesthetized Yorkshire swine.

Relevant Findings

The median dose was 200ul. Three animals in the control group and four in the treatment group required electrical conversion for episodes of ventricular fibrillation (VF) during ischemic occlusion. Use of increasing amounts of gel had longer ischemic times. Three animals in the control group and four in the treatment group

required electrical conversion for episodes of ventricular fibrillation (VF) during ischemic occlusion.

Study# 2: A non-GLP 3-hour comparative safety study in anesthetized, nifedipine-treated juvenile Landrace/Yorkshire swine.

Relevant Findings

The ventricular fibrillation rate was 3/6 swine (50%) and required multiple episodes of cardio conversion of between 7 and 15 attempts of 10-30 joules each attempt. One mortality occurred due to ventricular fibrillation. Cardiac CK-MB increased in all animals from baseline to sacrifice (0.23+/-.05 to 0.82 +/-.33). Troponin-T increased only in animals that were cardio converted (.01ng/ml to .02, .25, and 25.7 ng/ml each of the three who fibrillated). Mean occlusion time for Legoo was 11.3 +/-2.1 minutes and for shunt occlusion 23.5 +/- 15.9 minutes. There were no gross myocardial changes. Histologically the study demonstrated that a lack of ischemic or infarction complications distally to the bypassed arteries. The results indicate that the gel did not cause alterations in the endothelium-dependent relaxations.

Study # 3: A Non-GLP product development and instructions for use study – Phase 1.

Relevant Findings

The experiments demonstrated that the particular polymer concentration and temperature did not impact safety and effectiveness of the device. In addition, the investigated concentrations, 20 w% and 22.5 w%, enabled occlusion times of 15 minutes. At both concentrations, occlusions reopened with ice after 15 minutes. Only 2 animals from the embolized group of 4 were evaluable to not do anatomic exclusions.

Study # 4: A Non-GLP product development and instructions for use study – Phase 2.

Relevant Findings

The effectiveness of 200ul LeGoo for temporary arterial occlusion was confirmed. Reopening of the vessel with ice was always effective. LeGoo seems to be as effective in non-disease arteries as arteries induced with stenosis.

Study # 5: A -GLP pre-clinical sub chronic safety study in control (vessel-loops) or LeGoo-models of coronary arteriotomy- juvenile Yorkshire/Landrace swine.

Relevant Findings

There was one death in the treatment group from ventricular fibrillation inconclusively disassociated from test article or the procedure. The CK-MB remained steady throughout the study and Troponin-T was elevated equally in both groups following ischemia and subsided near baseline in 3 days. There were no statistically significant differences in the rate of observations between the treatment and control group. Subgross assessment of the heart tissue did not demonstrate any changes consistent with areas of non-vital (infarcted)

myocardium in either the treatment or the control group. The results indicate that the gel does not cause myocardial infarct when used to clamp the LAD.

Study # 6 Pre-clinical subchronic GLP safety and effectiveness with controls to demonstrate safety and effectiveness during OPCAB

Relevant Findings
Three animals of 10 died in the test group and one of 10 in the control group. In the test group, one animal died post procedure in the surgery suite from ventricular fibrillation following occlusion, one in recovery from bradycardia and hypotension, and one on sedation at the 7-day terminal study anesthetic episode who had listed a root cause of pericardial bleeding, effusion, and tamponade. Clinical pathology was within normal limits in both study groups. Cardiac ultrasonographic evaluation was confounded by technical limitations of the study.

X. SUMMARY OF PRIMARY CLINICAL STUDIES

A. Study design

Feasibility Study
To evaluate the safety and effectiveness of LeGoo for its ability to provide temporary coronary occlusion and hemostasis during Minimally Invasive Direct Coronary Artery Bypass (MIDCAB) surgery. Between January 2009 and March 2009, 20 consecutive MIDCAB patients were studied. Ten patients received a conventional MIDCAB procedure using proximal vessel loops and CO_2 blower (control group). The following 10 patients were operated by an otherwise identical procedure, except that intracoronary administration of LeGoo was used instead of vessel snares (LeGoo group). Left Internal Mammary Artery (LIMA) bypass flow, peri- and postoperative events and perioperative creatinine kinase-MB fraction (CK-MB) release were prospectively analyzed. CO_2 blower use was required in three of 10 of the LeGoo patients. Procedural time was identical, with a trend of shorter anastomosis time in the LeGoo group (12.3 vs. 10.7 min). LIMA-LAD flow was also not different (control 35.8 vs. LeGoo 42.5 ml/min, P=0.541). CK-MB values were not statistically different on postoperative days 1 and 2. However, the level of CK-MB 4 hours postoperatively was lower in LeGoo patients (18.3 ± 6.1 vs. 13.2 ± 2.9 U/L). No major adverse cerebral or cardiovascular event occurred postoperatively and during follow-up of 317 ± 21 days. There were no negative postoperative events associated with the use of LeGoo.

Pivotal Study
A prospective, randomized, multi-center (Canada, France, Germany, Netherlands) clinical trial with a minimum target of 110 eligible study subjects (55 in each group) undergoing Off Pump Coronary Artery Bypass (OPCAB) was conducted. The purpose of this study was to assess the clinical effectiveness (primary endpoint) and safety of LeGoo in comparison to a standard vessel occlusion method (i.e.

vessel loops). There were nine investigational sites. This study specifically focused on the use of LeGoo in OPCAB. Pluromed's pivotal clinical study has complied with ISO 14155-1:2003 Clinical Investigation of Medical Devices for Human Subjects – Part 1.

1. Clinical Inclusion and Exclusion Criteria

This study included subjects undergoing OPCAB surgery who were judged by the operating surgeon to be low-risk candidates for OPCAB and excluded any subjects meeting high-risk criteria.

Inclusion criteria

- Subjects undergoing elective off pump coronary artery bypass (OPCAB) surgery where the surgeon prospectively plans to use a vascular occlusion device
- >70% proximal stenosis of at least one target coronary artery, other than left main
- Age: 18 -79 years old
- Gender: male and female
- Subject is willing and able to participate in a clinical research study and provides informed consent
- Subject is able and willing to participate in required follow-up procedures

Exclusion criteria

- Previous cardiac surgery
- Left ventricular dysfunction (EF <40%)
- >50% of left main coronary artery stenosis
- Subjects with a logistic EuroScore equal to or greater than 10% as calculated by the euroscore.org calculator
- Emergent Surgery: Subjects undergoing surgery before the start of the next working day following catheterization
- Creatinine > 200 μmol/L
- Bilirubin > 21 μmol/L
- Subjects with chronic pulmonary disease [FEV1 < 45%.]
- Any subject who is deemed by the investigator, for any reason, not suitable or able to participate in a research study
- Pregnant women. Women of childbearing age will require a pregnancy test within 10 days of the operation and will be excluded if the result is positive.
- Women who are lactating
- Subjects who have undergone other investigational therapy within 30 days prior to the operation or who are scheduled to receive investigational therapy within 6 months of the operation
- Subjects suspected to have one intra-myocardial artery among the coronary arteries to bypassed during that surgery

2. Follow-up Schedule

A follow up assessment 3 – 7 weeks post-operative included assessing the subject relevant to the composite safety measurement. Subjects who were discharged and did not return for follow-up were contacted and attempts to reschedule appointments were made.

3. Clinical Endpoints

The primary effectiveness endpoint, satisfactory hemostasis, was determined by surgical observation. The secondary effectiveness endpoint, duration of anastomosis, was determined by time measurement.

Safety was measured as a composite of four Major Adverse Cardiac Events (MACE) : death, graft occlusion, myocardial damage, and low post procedure cardiac output. Myocardial damage defined per European Society of Cardiology – American College of Cardiology – American Heart Association – World Heart Federation (ESC-ACC-AHA-WHF) Guidelines for the Application of the Universal Definition. The primary safety objective was to show that LeGoo is non-inferior to the control (vessel loops) in the composite MACE rate at 30-day post procedure with a one-sided significance level of 0.025 and non-inferiority margin of 10% using the exact test.

Safety Composite Endpoint

The safety assessment is a composite of 4 Major Adverse Cardiac Events (MACE): death, graft occlusion, myocardial damage, and low post procedure cardiac output.. The primary safety objective was to show that LeGoo is non-inferior to the control (vessel loops) in the composite MACE rate at 30-day post procedure with a one-sided significance level of 0.025 and non-inferiority margin of 10% using the exact test.

$$H_o : \pi_1 - \pi_0 \geq 0.10$$
$$H_a : \pi_1 - \pi_0 < 0.10$$

where π_1 and π_0 are the composite MACE rate for LeGoo and the control, respectively

The primary effectiveness endpoint, satisfactory hemostasis, was defined by the surgeon who quantified his/her observation about the quality of the surgical field using the following scoring system:

- Excellent hemostasis (no bleeding)
- Minimal bleeding (bleeding does not interfere with suturing)
- Modest bleeding (required intermittent use of another device to control bleeding at the site of the anastomosis)
- Copious bleeding (required continuous use of another device)

"Excellent hemostasis" and "minimal bleeding" were considered "satisfactory hemostasis." Satisfactory hemostasis constituted a treatment success for the purpose of evaluating the primary effectiveness endpoint, the proportion of anastomoses in which satisfactory hemostasis was achieved.

The secondary effectiveness endpoint was total duration of anastomosis, including the time necessary for ensuring vessel occlusion. The other outcomes measured for descriptive purposes were:

- Blood loss during surgery
- Time required to occlude the vessel
- Number of units transfused
- Last hemoglobin measurement

Analysis of effectiveness, result summary and statistical conclusion
Primary Effectiveness – Satisfactory Hemostasis per Anastomosis, Analyzed by Generalized Estimating Equation (GEE). The primary effectiveness objective was to show that LeGoo is non-inferior to the standard control (vessel loops) in the proportion of anastomosis with satisfactory hemostasis with a one-sided significance level of 0.025 and non-inferiority margin of 10% using GEE that adjusts for correlation between multiple anastomoses within a subject (with exchangeable correlation structure).

$$H_o : \pi_1 - \pi_0 \leq -0.10$$
$$H_a : \pi_1 - \pi_0 > -0.10$$

where π_1 and π_0 are the proportions of satisfactory hemostasis for LeGoo and the control, respectively.

The estimates of the probability of successful hemostasis were calculated by back transforming the Logit estimates the probability scale

B. <u>Accountability of PMA Cohort</u>

At the time of database lock, of 110 patients enrolled in PMA study, 95% patients were available for analysis at the completion of the study (March 2, 2010) post-operative visit.

The table below describes the disposition and accountability of all subjects.

Table 7. Subject Accountability

	LeGoo	Control
Treated (As-Treated)	56	54
Followed to 1 Month	54	51
Reasons for Early Discontinuation		
Death	1	0
Withdraw of consent	0	1
Lost to follow-up	0	2
Subject refused follow-up	1	0

C. **Study Population Demographics and Baseline Parameters**

Demographic and baseline characteristics for the total study population are described in the tables that follow for demographics; pre-operative vital signs, anticoagulation, medical history, clinical laboratory values, cardiac measurements; and calculation of the pre-operative logistic EuroSCORE.

Table 8. Demographics

	LeGoo			Control	
		Mean ±std (median)	**Range**	**Mean ±std (median)**	**Range**
Age (yrs)		63.9 ±9.9 (65.0)	37, 79	64.2 ±8.4 (65.0)	39, 79
Height (cm)		170.4 ±8.0 (170.0)	149, 189	171.5 ±8.2 (172.0)	149, 193
Weight (kg)		84.0 ±15.5 (83.0)	49, 121	82.7 ±14.9 (85.0)	55, 110

	Frequency	**95% CI**	**Frequency**	**95% CI**
Male	82% (45)	69%, 91%	84% (46)	71%, 92%
Female	18% (10)	9%, 31%	16% (9)	8%, 29%

Demographics were similar between LeGoo and Control subjects.

Table 9. Pre-operative Vital Signs

	LeGoo		Control	
	Mean ±std (median)	**Range**	**Mean ±std (median)**	**Range**
Heart rate (bpm)	66.2 ±9.8 (65.0)	45, 90	70.3 ±15.0 (66.0)	45, 130
Respiratory rate (bpm)	15.4 ±4.1 (15.0)	9, 25	15.2 ±3.6 (15.0)	10, 23
Blood pressure				
Systolic (mmHg)	135.1 ±18.8 (140.0)	97, 170	129.0 ±22.3 (125.0)	88, 197
Diastolic (mmHg)	75.1 ±10.6 (75.0)	57, 100	74.9 ±10.8 (70.0)	52, 102
Temperature (°C)	36.5 ±0.4 (36.5)	35.0, 37.6	36.4 ±0.4 (36.4)	35.3, 37.0

Vital signs were similar between LeGoo and Control subjects.

Table 10. Pre-operative Anticoagulation

	LeGoo	Control
	Frequency	**Frequency**
Anticoagulation – Yes	80% (44)	82% (45)

Anticoagulation frequency was similar between LeGoo and control subjects.

Table 11. Pre-operative Medical History

	LeGoo	Control
	Frequency	Frequency
Dyspnea	45% (25)	36% (20)
Syncope	4% (2)	7% (4)
Palpitations	7% (4)	11% (6)
Other relevant to cardiac health	13% (7)	16% (9)
Diabetes	29% (16)	16% (9)
Hypertension	78% (43)	76% (42)
Peripheral Vascular Disease including aneurysm	13% (7)	25% (14)
Drug or alcohol abuse	2% (1)	5% (3)
Congestive heart failure	80% (44)	85% (47)
NYHA Class I	23% (10)	28% (13)
NYHA Class II	39% (17)	38% (18)
NYHA Class III	34% (15)	34% (16)
NYHA Class IV	5% (2)	0% (0)
History of angina pectoris	85% (47)	96% (53)
CCS Class I	4% (2)	9% (5)
CCS Class II	53% (25)	49% (26)
CCS Class III	34% (16)	32% (17)
CCS Class IV	9% (4)	9% (5)
Other cardiac pathology	7% (4)	9% (5)

Medical history was similar between LeGoo and Control subjects, with the following exceptions: LeGoo subjects had a higher frequency of diabetes than Control subjects (29% vs. 17%), and Control subjects had a higher rate of peripheral vascular disease (PVD) than LeGoo subjects (26% vs. 13%).

Table 12. Pre-operative Clinical Laboratory Values

	LeGoo		Control	
	Mean ±std (median)	**Range**	**Mean ±std (median)**	**Range**
Creatinine (µmol/L)	86.0 ±20.5 (85.0)	46.0,155.0	82.2 ±18.5 (79.0)	44.2, 132.0
Bilirubin (µmol/L)	10.7 ±5.8 (9.0)	3.4, 29.9	10.2 ±5.2 (9.0)	2.7, 31.0
Hemoglobin (g/dL)	13.6 ±2.0 (14.1)	8.4, 17.0	13.8 ±1.8 (14.0)	9.1, 16.7

Cardiac enzymes, which were quantified with different units of measure at the various sites, are listed in the table below. Only one enzyme was required to be measured; either troponin I or the CK-MB / total CK ratio. In 27 subjects, only total CK was measured. In 1 Subject, no cardiac enzymes were measured.

Table 13. Baseline Cardiac Enzymes

	LeGoo		Control	
	Mean ±std (median)	**Range**	**Mean ±std (median)**	**Range**
Troponin I (pg/L)	0.05 ±0.13 (0.02)	0.00- 0.73	0.02 ±0.02 (0.02)	0.00 – 0.10
CK-MB (U/L)	32.70 ±62.64 (12.30)	1.60 – 186.50	14.41 ±18.37 (11.60)	1.80 – 61.20
CK-MB (ng/mL)	2.59 ±1.57 (2.60)	0.70 – 5.60	2.46 ±0.60 (2.20)	1.90 – 3.40
Total CK (U/L)	28.03 ±35.18 (12.00)	1.00 – 119.00	47.20 ±112.52 (9.00)	2.00 – 626.00
Total CK (µmol/L)	1.00 ± n/a (1.00)	1.00 – 1.00	1.00 ± n/a (1.00)	1.00 – 1.00

In general, clinical laboratory results were similar between LeGoo and control subjects. CK-MB (U/L) was more than twice as high for LeGoo than Control subjects, but appears to be due to an outlier.

Pre-operative Cardiac and Pulmonary Measurements

Table 14. Baseline Cardiac and Pulmonary Measurements

	LeGoo	Control
	Frequency	**Frequency**
Abnormal Q wave[1]	20% (11)	9% (5)
Arrhythmia	20% (11)	11% (6)
Atrial Fibrillation	5% (3)	7% (4)
Life Threatening Ventricular Arrhythmias	2% (1)	0% (0)
MI in previous 90 days	13% (7)	7% (4)
Abnormal wall motion	25% (14)	13% (7)
	Mean ±std (median)	**Mean +/-std (median)**
Pulmonary artery pressure systolic	26.8 ±6.2 (27.0)	29.4 ±7.9 (29.5)
LV ejection fraction	61.3 ±11.3 (64.0)	60.5 ±9.0 (60.0)
FEV_1 percent	90.9 ±18.1 (87.9)	92.7 ±22.0 (91.0)

Non-similarity between Groups in Baseline Cardiac Measurements

LeGoo subjects had approximately a two-fold higher frequency in 4 of the 6 measurements of abnormal cardiac function or cardiac damage, abnormal Q wave, arrhythmia, MI in previous 90 days and abnormal wall motion. This results in a difference in the clinical profile between LeGoo and control subjects, with the LeGoo subjects having a more serious clinical picture at baseline. These baseline clinical differences did not result in any difference in preoperative mortality risk assessment as judged by EUROSCORE (Table 15).

Table 15 Baseline Logistic EuroScore

	LeGoo		Control	
	Mean ±std (median)	**Range**	**Mean ±std (median)**	**Range**
EuroScore percent	2.3 ±1.8 (1.8)	0.6, 8.6	2.5 ±1.5 (2.1)	0.9, 7.6

D. Safety and Effectiveness Results

1. Safety Results

Table 18. Safety Composite Endpoint

	LeGoo	Control
	Frequency	**Frequency**
Composite Safety Index	**6.3% (3)**	**6.5% (3)**

Six subjects experienced at least one of the four events within the MACE index: three LeGoo and three Control subjects. One LeGoo subject reported all four elements of the MACE safety composite index. This was the only patient death in the study. Based on review of the clinical data it was presumed to be the result of Heparin Induced Thrombocytopenia (HIT).

Table 19. Elements of Safety Composite *Endpoint*

	LeGoo	Control
Safety Element	**Frequency**	**Frequency**
Graft Occlusion	3	0
Myocardial Damage[1]	1	1
Low post procedure cardiac output	1	2
Death	1	0

[1] Myocardial damage defined per ESC-ACC-AHA-WHF Guidelines for the Application of the Universal Definition.

, The analysis of serious adverse events, adverse events and of an index of Major Adverse Cardiac Events suggests that LeGoo is non-inferior to vessel loops.

Adverse Events that occurred in the PMA clinical study

A summary of adverse events (AEs) classified by System Organ Class is included below: non-serious adverse events in Table 20; serious adverse events in Table 21. The serious adverse events (SAEs) are a subset of the AEs, that is, Table 21 includes those AEs from Table 20 that were judged by the investigators as meeting the definition of serious, predefined in the study as including: death; life-threatening or permanently disabling events; or those that required prolonged hospitalization. If the outcome was death, the death was classified as occurring: during OPCAB; post OPCAB but pre-discharge; or post-discharge.

At least one AE was reported in 43/56 (76.8%) LeGoo and 33/54 (61.1%) control subjects; no AEs were reported in 13/56 (23.2%) LeGoo and 21/54 (38.9%) Control subjects. No unanticipated AEs were reported. There were no device failures or replacements.

At least one SAE was reported in 16/56 (28.6%) LeGoo and 8/54 (14.8%) Control subjects. No SAEs were reported in 40/56 (71.4%) LeGoo and 46/54 (85.2%) Control subjects. The levels and types of SAEs reported in this clinical study were anticipated and are similar to those reported in similar sized studies of major cardiac procedures .

One SAE was shown to be inconclusive as to whether it was related to the study device.

Table 20. Adverse Events reported including SAEs.

	LeGoo N=56		**Control N=54**	
System Organ Class	Events	Patients with Events	Events	Patients with Events
No Adverse Events	-	13 (23.2%)	-	21 (38.9%)
At Least One Adverse Event	139	43 (76.8%)	115	33 (61.1%)
Blood and lymphatic system disorders	5	5 (8.9%)	3	3 (5.6%)
Cardiac disorders	37	29 (51.8%)	21	19 (35.2%)
Endocrine disorders	0	0 (0%)	1	1 (1.9%)
Gastrointestinal disorders	13	9 (16.1%)	6	5 (9.3%)
General disorders and administration site conditions	16	11 (19.6%)	10	9 (16.7%)
Infections and infestations	8	7 (12.5%)	5	5 (9.3%)
Injury, poisoning and procedural complications	11	10 (17.9%)	14	11 (20.4%)
Investigations	2	2 (3.6%)	5	5 (9.3%)
Metabolism and nutrition disorders	4	3 (5.4%)	7	5 (9.3%)
Musculoskeletal and connective tissue disorders	2	2 (3.6%)	0	0 (0%)
Nervous system disorders	5	4 (7.1%)	1	1 (1.9%)
Psychiatric disorders	7	6 (10.7%)	6	6 (11.1%)
Renal and urinary disorders	3	3 (5.4%)	6	4 (7.4%)

System Organ Class	LeGoo N=56 Events	LeGoo N=56 Patients with Events	Control N=54 Events	Control N=54 Patients with Events
Respiratory, thoracic and mediastinal disorders	20	14 (25%)	21	14 (25.9%)
Skin and subcutaneous tissue disorders	3	3 (5.4%)	1	1 (1.9%)
Surgical and medical procedures	0	0 (0%)	1	1 (1.9%)
Vascular disorders	3	2 (3.6%)	7	5 (9.3%)

Table 21 – Serious adverse events reported

	LeGoo (N=56)		Control (N=54)	
System Organ Class	Events	Subjects with Events	Events	Subjects with Events
At Least One Serious Adverse Event	19	16 (28.6%)	11	8 (14.8%)
No Adverse Events	0	40 (71.4%)	0	46 (85.2%)
Cardiac disorders	9	9 (16.1%)	3	2 (3.7%)
General disorders and administration site conditions	3	3 (5.4%)	1	1 (1.9%)
Infections and infestations	0	0 (0%)	2	2 (3.7%)
Injury, poisoning and procedural complications	7	6 (10.7%)	3	3 (5.6%)
Investigations	0	0 (0%)	1	1 (1.9%)
Respiratory, thoracic and mediastinal disorders	0	0.(0%)	1	1 (1.9%)

2. Effectiveness Results

Table 16. Primary Effectiveness – Satisfactory Hemostasis per Anastomosis

	LeGoo			Control		
	N	**Probability of Satisfactory Hemostasis**		**N**	**Probability of Satisfactory Hemostasis**	**P-Value**
Satisfactory: Intent-to-treat	121[1]	86%		123[2]	61%	<0.0001
Satisfactory: Completed cases	116[1]	87%		116[2]	63%	<0.0001
Satisfactory: As-treated	117[3]	88%		122	61%	<0.0001

Anastomosis time

The data indicates a shorter time to anastamosis in the treatment arm compared to the control arm.

Table 18. Secondary Effectiveness – Duration of Anastomosis

	Duration of the anastomosis		P value
	LeGoo N=121	Control N=127	
Duration of anastomosis, total, min	12.8 ± 4.7	15.4 ± 6.1	<0.001
to LAD/diagonal territory, min	12.9 ± 4.9	14.4 ± 5.3	
to marginal/circumflex territory, min	12.2 ± 3.7	16.1 ± 5.6	
to RCA/PDA territory, min	13.8 ± 6.1	17.6 ± 8.2	

Table 19. Primary Efficacy – Satisfactory Hemostasis per Anastomosis by Gender

	LeGoo			Control		
	N	Probability of Satisfactory Hemostasis	95% CI	N	Probability of Satisfactory Hemostasis	95% CI
Overall: As-treated	117	88%	80%, 93%	122	61%	50%, 71%
Male	101	89%	81%, 94%	101	59%	47%, 70%
Female	16	77%	54%, 91%	21	68%	40%, 87%

Table 20. Duration of Anastomosis by Gender

	Duration of the anastomosis	
	LeGoo N=116	Control N=118
Duration of anastomosis, total (min)	12.8 ± 4.7	15.1 ± 5.9
Male	12.6 ± 4.7 N=101	15.2 ± 6.1 N=97
Female	14.2 ± 4.4 N=15	14.7 ± 4.3 N=21

XI. PANEL MEETING RECOMMENDATION AND FDA'S POST-PANEL ACTION

In accordance with the provisions of section 515(c)(2) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Circulatory System Devices Panel, an FDA advisory committee, for review and recommendation.

XII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Safety Conclusions

Safety was determined by the analysis of serious adverse events, adverse events and of an index of Major Adverse Cardiac Events. Based on the data, it suggests that LeGoo is safe compared to the control. The study was conducted in surgeries of the cardiovascular bed, where adverse events are well known and well documented through other devices studies. Use in the cardiac vascular bed also represents a worst case situation to support use for temporary vascular occlusion of below the neck vessels up to and including 4 mm in diameter.

B. Effectiveness Conclusions

Based on the data, LeGoo demonstrated satisfactory hemostasis and non-inferiority to the control. The study data also indicates that the use of LeGoo results in shorter anastomosis times.

C. Overall Conclusions

The data in this application support the reasonable assurance of safety and effectiveness of the device when used in accordance with the indication for use. The clinical evidence demonstrates that LeGoo achieves its intended performance of vessel occlusion to achieve and maintain satisfactory hemostasis during normal conditions of use.

This study specifically focused on the use of LeGoo in off-pump coronary bypass (OPCAB), as a most sensitive model of adverse changes that may occur at any vascular site. Given cardiac tissue is the most sensitive of the end organs; it is acceptable to use this in peripheral areas. The expected dose range in peripheral vessels is comparable and the risk of end organ damage is much lower due to an increased tolerance to ischemia in non cardiac tissues below the neck

XIII. CDRH DECISION

CDRH issued an approval order on September 28, 2011.

The applicant's manufacturing facilities were inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820).

XIV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the device labeling.

Post-approval Requirements and Restrictions: See approval order.