Summary of Safety and Effectiveness Data (SSED)

[Revision date: January 29, 2009]

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1 General Information

Generic Name:	SuperSaturated Oxygen Therapy
Device Trade Names:	TherOx® Downstream® AO System Model number: AOSY 1
	TherOx® Downstream® AO Cartridge Model number: AOCR 1
	TherOx® MI-Cath™ Infusion Catheter Model number: MI-1
Applicant's Name and Address:	TherOx, Inc. 17500 Cartwright Rd. Suite 100 Irvine, CA 92614
PMA Application Number:	P080005
Date(s) of Panel Recommendation:	
Date of Notice of Approval to Applicant:	

2 Indications for Use

The TherOx® Downstream® AO System, Downstream® AO Cartridge, and MI-Cath™ Infusion Catheter are indicated for: The preparation and delivery of SuperSaturated Oxygen Therapy (SSO_2 Therapy) to targeted ischemic regions of the patient's coronary vasculature immediately following revascularization by means of percutaneous coronary intervention (PCI) with stenting that has been completed within 6 hours after the onset of anterior acute myocardial infarction (AMI) symptoms.

3 Patient Selection Criteria

- Less than 6 hours from symptom onset to successful reperfusion by means of PCI with stenting of an anterior ST-elevation AMI.
- Target artery $\geq$ 2 mm in diameter.
- TIMI flow grade $\geq$ II in target artery after successful revascularization by means of PCI with stenting.
- Patient has anticoagulation regimen during administration (ACT > 250 seconds or equivalent per physician practice).
- Systemic arterial pO_2 greater than or equal to 80 mmHg with supplemental oxygen.

4 Contraindications

- Ipsilateral insertion of a second sheath in a single femoral artery for SuperSaturated Oxygen Therapy is strictly contraindicated.
- Proximal coronary stenosis that restricts flow with the infusion catheter in place.
- Presence of a post-intervention non-stented coronary dissection or perforation.
- Cardiac valvular stenosis or insufficiency and pericardial disease.
- Pregnancy.
- Patients contraindicated for anticoagulation therapy.

5 Warnings and Precautions

Summary of Warnings

- Only physicians who have received appropriate training in the use of the Downstream AO System should perform SuperSaturated Oxygen Therapy (SSO_2 Therapy).
- SuperSaturated Oxygen Therapy must be initiated and should be completed in the cardiac catheterization laboratory.
- The Downstream AO System may not be operated concomitantly with magnetic resonance imaging.
- Use aseptic technique throughout procedure.
- Provide adequate anticoagulation prior to and during therapy per clinical practice standards.
- Inspect the Downstream AO Cartridge and packaging for damage prior to use; do not use if the cartridge or packaging is damaged.

- Do not use any type of infusion catheter for SSO_2 Therapy delivery other than the MI-Cath Infusion Catheter. Inspect the infusion catheter and packaging for damage and kinking prior to use; do not use if the catheter or packaging is damaged.
- If resistance is felt at any time, DO NOT force passage of the MI-Cath Infusion Catheter. Resistance may indicate a problem and may result in damage to the vessel or the catheter if passage is forced. Determine the cause of the resistance and take any necessary remedial action.
- After placement, inspect the infusion catheter under fluoroscopic visualization to ensure that it is seated correctly in the target artery and does not restrict blood flow.
- Do not disengage the guide catheter unless there is flow through the MI-Cath Infusion Catheter.
- Verify that all tubing connections on the Downstream AO Cartridge are secure and tight prior to initiating prime.
- Verify that the return tubing of the cartridge is not connected to the infusion catheter prior to initiating prime.
- The bubble detector is disabled during prime. Ensure that return tubing is fully blood primed with no presence of air or bubbles in the line prior to making wet-to-wet connection to the infusion catheter.
- Do not re-use the single-use Downstream AO Cartridge and MI-Cath Infusion Catheter.
- Dispose of used Downstream AO Cartridges and MI-Cath Infusion Catheters using standard hospital procedures to eliminate hazardous waste.
- Only qualified personnel trained in oxygen safety and handling should change the oxygen bottle.
- Do not exceed the SSO_2 Therapy cumulative duration of 90 minutes when using multiple cartridges.

Summary of Precautions

- If less than a 2F difference exists between guide catheter and introducer sheath (coaxial approach) or less than 4F access is used on contralateral draw site, SSO_2 Therapy may stop from excessive negative draw pressure.
- Ensure that hands are clean and free of oil, lotion, or any kind of lubricant when handling the oxygen regulator, regulator seal, oxygen knob, Downstream AO Cartridge, and the cartridge compartment of the AO System.
- Do not use the Downstream AO System if the oxygen bottle pressure is less than 800 psig (54.4 bar).
- Do not expose electrical connections, including the transducer jack, to fluid contact.
- Do not stretch the return tubing while loading into the detectors.
- Ensure that the return tubing is fully seated in the detector slots before latching to prevent the detector doors from pinching the tubing.
- Do not over-torque the hemostasis valve onto the infusion catheter; over-torquing may kink and occlude the infusion catheter.
- Do not flush fluoroscopic contrast agents through the infusion catheter; these viscous solutions may result in an over-pressure fault after connection to the cartridge return tubing is made.
- Flush blood sample port with heparinized saline before connections are made.
- If the return pressure reaches 2000 mmHg during prime, the pump will stop. If this occurs, release the prime button and unload the cartridge. Load a new cartridge and verify that the tube set and infusion catheter are free of kinks before initiating prime.
- Ensure that draw and return lines are neither kinked prior to starting prime nor during any other time during use.
- Tap (flick) the pressure transducers while priming (prior to making the wet-to-wet connection) to dislodge trapped bubbles. Take particular care to completely de-bubble the transducer on the return line.
- Do not open the pump head while blood is circulating.
- Do not open the sample port stopcock on the Downstream AO Cartridge tubing unless a syringe is attached.
- If the WARNING LOW BATTERY message is displayed, plug the Downstream AO System into an electrical outlet within 5 minutes, clear the warning, and finish the procedure using AC power.

6 Device Description

The TherOx Downstream AO System is a Class III medical device that infuses highly oxygen-enriched blood directly to the heart's target coronary artery after treatment for an anterior acute myocardial infarction (AMI). The procedure is adjunctive to target vessel revascularization by percutaneous coronary intervention (PCI). Anterior AMI patients who receive PCI within six hours of symptom onset are eligible to receive the procedure.

Oxygen enrichment of autologous arterial blood is accomplished in two stages. The first step creates a liquid solution of hyper-elevated concentrations of oxygen dissolved in sterile saline. This oxygen-concentrated saline solution is termed SuperSaturated oxygen solution or SSO_2 solution. SSO_2 solution then is mixed in an extracorporeal circuit with circulating arterial blood and delivered directly to the coronary arteries through an infusion catheter.

The procedure, referred to as SuperSaturated Oxygen Therapy or SSO_2 Therapy, is adjunctive to the successful revascularization of the AMI target artery by percutaneous coronary intervention (PCI) with stenting. SSO_2 Therapy is incorporated into the treatment regimen of the Cardiac Catheterization Laboratory (cath lab) and is performed under the supervision of the interventional cardiologist. SSO_2 Therapy follows successful PCI and does not delay primary intervention to open the blocked target artery. The duration of SSO_2 Therapy is ninety (90) minutes.

The apparatus (equipment) for SSO_2 Therapy includes a hardware device called the TherOx® Downstream® AO System ("AO System"), a single-use device called the TherOx® Downstream® AO Cartridge ("AO Cartridge") and a sterile, single-use intravascular catheter called the TherOx® MI-Cath™ Infusion Catheter ("Infusion Catheter"). The AO System hardware controls the performance of the AO Cartridge, operates the extracorporeal flow circuit, and performs safety monitoring based upon measured inputs. The AO Cartridge has a housing and tubing set; patient arterial blood is pumped into the draw tubing by the AO System, the blood oxygen concentration is elevated with SSO_2 solution in the cartridge housing, and the blood is returned to the patient through the return tubing and infusion catheter. The AO Cartridge draw tubing connects to a patient arterial sheath on the draw side, and the return tubing connects to the Infusion Catheter to form a closed-loop extracorporeal circuit. The Infusion Catheter is placed over a guidewire through a guide catheter into the coronary artery by an interventional cardiologist (physician). **Figure 1** displays a schematic representation of the extracorporeal flow circuit for SSO_2 Therapy.

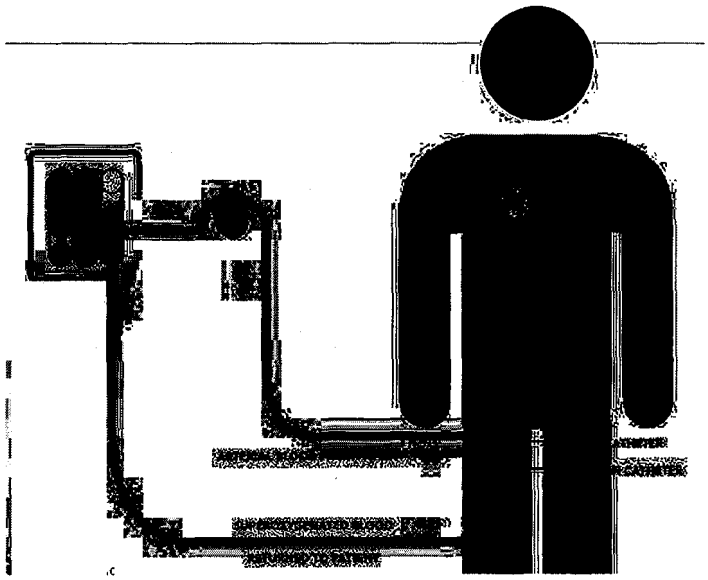

Figure 1. Schematic Representation of SSO_2 Therapy

The AO System

The AO System (Model Number AOSY-1) is the medical electrical device (console) that controls the AO Cartridge and monitors performance and safety during administration of SSO_2 Therapy. The AO System has a touch-screen display interface to guide the health care professional through setup and clinical operation. The system is non-sterile and has no direct patient contact. The AO System is intended primarily to be mains operated (AC-powered) and stationary during use, but it has handles and wheels to facilitate movement and is internally powered by a battery for operation during transport. The AO System is 62 inches tall, 26 inches wide at its handles, and 26 inches deep at its base. The system weighs 280 lbs and is operated by a standing user. The AO System has several integrated subsystems mounted upon a single system chassis. These subsystems include a console to control AO Cartridge mixing and metering operations, a peristaltic blood pump with flow-feedback control, a user-interface touch screen display, a power supply, an oxygen supply system, and a dedicated safety interlock with automatic shutdown capabilities in the event of a safety response triggered by one of the subsystems. The AO System has active pressure, flow, air-in-line, and other monitored parameters to ensure safe operation. **Figures 2**, **3**, and **4** show schematic drawings of the AO System, including key features.

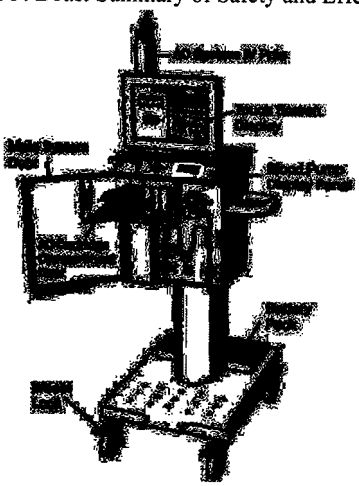

Figure 2. Downstream® AO System

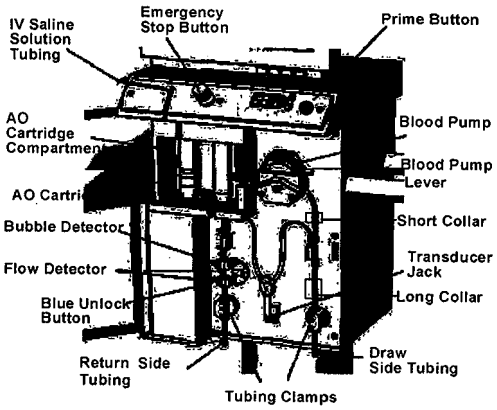

Figure 3. Close-up of System

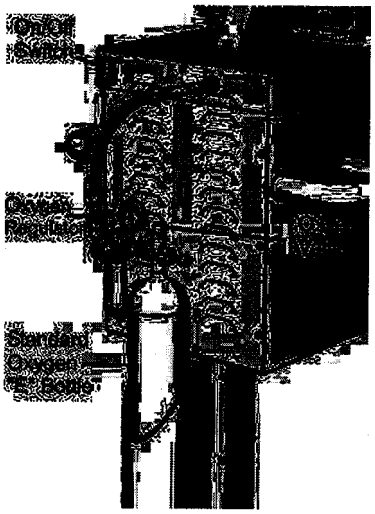

Figure 4. Back of System

The AO Cartridge

The AO Cartridge (Model Number AOCR-1) is a sterile, single-use device that is inserted in the AO System to support SSO_2 Therapy. The AO Cartridge, shown in **Figure 5**, comprises the blood-contact fluid flow path together with the Infusion Catheter. The AO Cartridge, when controlled by the AO System, creates SSO_2 solution from inputs of hospital-supplied oxygen gas and sterile saline solution. The AO Cartridge delivers and mixes autologous arterial blood from the patient with SSO_2 solution in a carefully designed extracorporeal circuit to create oxygen-enriched hyperoxemic blood with an elevated pO_2 level of 760 – 1000 mmHg. Because the SSO_2 solution has a high oxygen concentration, the flow rate of SSO_2 solution is only 3 ml/min out of a total return flow rate of 75 ml/min. Over 90 minutes, the total amount of infused saline is 270 ml.

The AO Cartridge weighs less than one pound and is constructed primarily from injection-molded polycarbonate. The tubing material is polyvinyl chloride (PVC). The draw and return tubing each have approximately 9 feet of working length. The blood priming volume of the AO Cartridge is approximately 60 ml. The AO Cartridge is individually packaged and has a validated three-year shelf life.

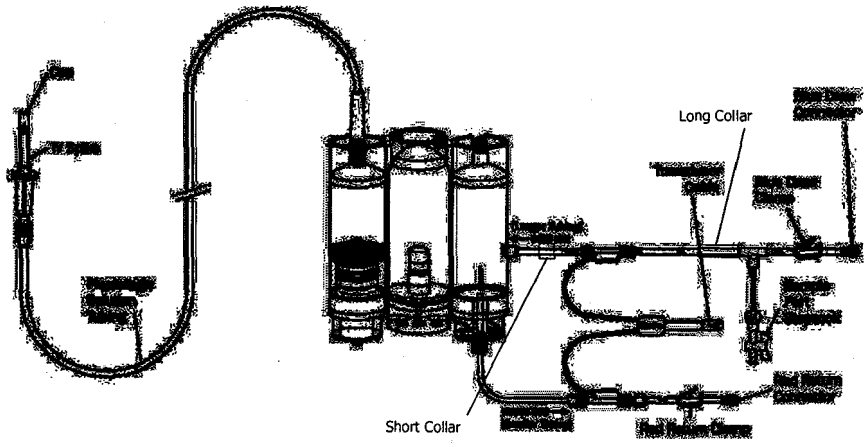

Figure 5. Downstream® AO Cartridge

The Infusion Catheter

The MI-Cath Infusion Catheter (Model Number MI-1) is a sterile, single-use over-the-wire device that may be inserted into the vasculature through commercially available guide catheters 6 F or larger. The Infusion Catheter is a single-lumen endhole catheter with a standard luer fitting at the proximal end for attachment to the return tubing of the AO Cartridge during the blood-priming step of SSO_2 Therapy administration. The catheter's outer diameter (O.D.) is 4.6 F along the working length. The catheter is extruded in a continuous process that transitions from a soft distal tip to the stiffer proximal shaft for optimal usability. The nominal usable length is 127 cm and the nominal overall length of the catheter is 135 cm. The inner diameter (I.D.) of the single lumen end-hole catheter is nominally 0.046 in. The catheter is individually packaged and has a three-year shelf life. The Infusion Catheter is the only qualified delivery catheter for SSO_2 Therapy. **Figure 6** shows a schematic of the Infusion Catheter.

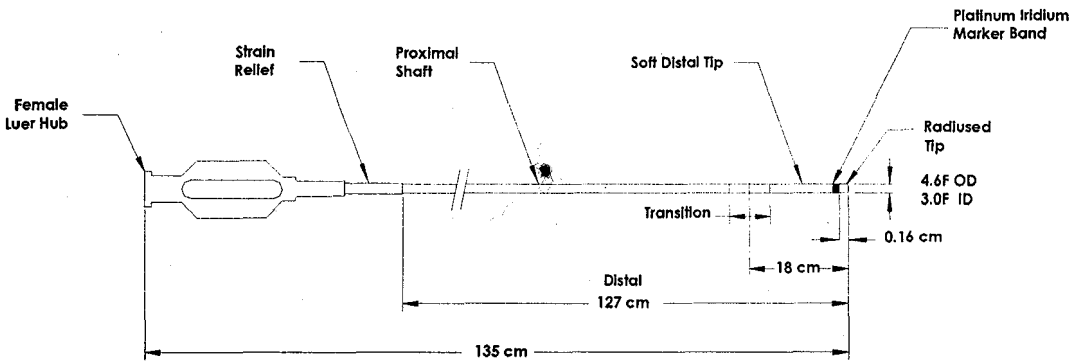

Figure 6. MI-Cath Infusion Cather

7 Alternative Practices and Procedures

SSO_2 Therapy is a novel treatment that seeks to deliver localized hyperbaric oxygen therapy directly to the target coronary arteries without impacting the systemic circulation. SSO_2 Therapy is adjunctive to PCI and augments the standard of care. No available therapeutic alternatives are known that seek to deliver focal oxygen-enriched blood for AMI.

The use of supplemental oxygen by means of nasal cannulae or an oxygen mask is routine in AMI care; the goal is to provide slightly increased systemic oxygen levels (but not hyperoxemic). Hyperbaric levels of blood oxygenation can be realized with the aid of hyperbaric chambers, but the use of these devices in AMI is strictly investigational and they have no labeling indication for this purpose.

8 Marketing History

The AO System, AO Cartridge, and Infusion Catheter[1] received CE-mark in September 2001 for sale in the European Community.

[1]The Infusion Catheter is CE-marked under the product name "AO Catheter" in Europe.

The first commercial AO System placement in Europe was October 20, 2001 in Italy. From that time until present, AO Systems and accessories have been sold in eight hospitals in two countries, including Italy and the Czech Republic. Currently, two hospitals in Italy are active commercial sites.

The AO System and required accessories have not been marketed in any other country or region outside of the European Community.

There have been no countries from which these devices have been withdrawn from marketing or subject to a recall action for any reason related to safety or effectiveness.

9 Adverse Events

SSO_2 Therapy is a cath-lab based procedure that is indicated for acute myocardial infarction patients who have undergone successful target vessel revascularization by means of PCI with stenting. The anticipated adverse events for the target patient population include those risks that would be present for anterior AMI patients, as well as risks that would be present for common interventional procedures.

The expected adverse events that may be seen in subjects undergoing SSO_2 Therapy are presented below, first listed in terms of potential adverse events based upon a comprehensive risk analysis of the procedure. Secondly, the observed adverse event profile is presented for the AMIHOT II trial.

9.1 Potential Adverse Events

The potential adverse events that may be observed in patients undergoing SSO_2 Therapy include hazards identified by an engineering risk analysis and the inherent condition of the patient population post-AMI. These adverse events are organized by severity and include:

- Death
- Acute Myocardial Infarction (AMI)
- Cardiogenic Shock
- Stroke/TIA
- Coronary Artery Occlusion
- Revascularization (CABG or PCI)
- Thrombosis
- Congestive Heart Failure
- Restenosis
- Tamponade
- Abrupt vessel closure/spasm
- Hemorrhage
- Embolism (including air emboli and thromboemboli)
- Aneurysm
- Arteriovenous Fistula/Pseudoaneurysm
- Arrhythmias
- Vascular damage (dissection, perforation, rupture, or other mechanical injury)
- Blood loss/damage
- Pericardial effusion
- Renal complications
- Pulmonary Edema
- Respiratory complications
- Hematoma
- Hemolysis
- Infection
- Allergic reactions
- Chest pain/angina
- Hypertension/Hypotension
- Neck/back/groin pain
- Nausea/Vomiting
- Anxiety / Dizziness

These adverse events are associated with interventional cardiology procedures. SSO_2 Therapy introduces no new or incremental adverse events other than those known to exist within the standard of care (PCI with stenting).

Based upon the extended time of cath lab intervention required for SSO_2 Therapy, the accompanying requirement for anticoagulation throughout the procedure, and the extracorporeal circuit, SSO_2 Therapy may increase the following specific risks:

- Air emboli
- Vascular damage from the placement of an infusion catheter
- Bleeding requiring treatment, particularly at the catheterization site

9.2 Observed Adverse Events

The safety of SSO_2 Therapy was evaluated during the 30-day study reporting period for Control patients and subjects receiving the superoxygenated infusion. The AMIHOT II study used the 30-day composite Major Adverse Cardiac Events (MACE) safety endpoint; MACE is the combined incidence of death, reinfarction, target vessel revascularization, and stroke. **Table 1** summarizes the MACE rate comparison between the Control and SSO_2 Therapy groups in an intent-to-treat (ITT) analysis. As seen in the table, the study MACE rates were comparable between the two study groups. A trend in slightly higher 30-day mortality and MACE was noted in the SSO_2 Therapy group as compared to Controls, but no significant differences were observed.

Table 1. AMIHOT II Primary MACE Safety Endpoint Events ≤ 30 days, ITT Analysis

	Randomization Group			
	Control (N=79)		**SSO_2 Therapy (N=222)**	
Adverse Event	**# of Events**	**# (%) of Pts with Events**	**# of Events**	**# (%) of Pts with Events**
Composite 30-Day MACE	5	3 (3.8%)	19	12 (5.4%)
Death	0	0 (0%)	4	4 (1.8%)
Target Vessel Revascularization[1]	3	3 (3.8%)	9	8 (3.6%)
Reinfarction	2	2 (2.5%)	6	4 (1.8%)
Stroke	0	0 (0%)	0	0 (0%)

[1]AMIHOT II main vessel or branches

During the 30-day follow-up period, 57/222 (25.7%) patients in the SSO_2 Therapy group and 15/79 (19.0%) patients in the Control group presented with one or more serious adverse events (SAEs). **Table 2** displays the summary of all observed SAEs during the 30-day follow-up period for both groups. SAEs are displayed both by System Organ Class (*e.g.*, Cardiac Disorders, Gastrointestinal Disorders) and for individual event codes. As seen in Table 2, 30-day SAE rates are nominally higher in the SSO_2 Therapy group as compared to Controls (25.7% vs. 19.0%), and the majority of events in both groups were classified as Cardiac Disorders, which also trended higher in the SSO_2 Therapy group (14.9% vs. 10.1%).

Table 2. Summary of All Serious Adverse Events within 30 Days

		Randomization Group			
Category	**Adverse Event**	**Control** (N=79)		**AO Therapy** (N=222)	
System Organ Class	**MedDRA PT**	**Events** (n)	**Pts with Events** (n/N; %)	**Events** (n)	**Pts with Events** (n/N; %)
Assessment Complete			79/79 (100.0%)		222/222 (100.0%)
Assessment Available†			79/79 (100.0%)		222/222 (100.0%)
All serious adverse events		19	15/79 (19.0%)	89	57/222 (25.7%)
BLOOD AND LYMPHATIC SYSTEM DISORDERS		0	0/79 (0.0%)	1	1/222 (0.5%)
	ANEMIA	0	0/79 (0.0%)	1	1/222 (0.5%)
CARDIAC DISORDERS		9	8/79 (10.1%)	41	33/222 (14.9%)
	ANGINA PECTORIS	1	1/79 (1.3%)	4	4/222 (1.8%)
	AORTIC VALVE STENOSIS	1	1/79 (1.3%)	0	0/222 (0.0%)
	ATRIAL FIBRILLATION	0	0/79 (0.0%)	1	1/222 (0.5%)
	CARDIAC ARREST	0	0/79 (0.0%)	1	1/222 (0.5%)
	CARDIAC FAILURE CONGESTIVE	4	4/79 (5.1%)	8	8/222 (3.6%)
	CARDIAC TAMPONADE	0	0/79 (0.0%)	1	1/222 (0.5%)
	CARDIOGENIC SHOCK	1	1/79 (1.3%)	5	5/222 (2.3%)
	CORONARY ARTERY DISEASE	1	1/79 (1.3%)	0	0/222 (0.0%)
	CORONARY ARTERY OCCLUSION	0	0/79 (0.0%)	1	1/222 (0.5%)
	CORONARY ARTERY STENOSIS	0	0/79 (0.0%)	1	1/222 (0.5%)
	MYOCARDIAL ISCHEMIA	0	0/79 (0.0%)	4	4/222 (1.8%)
	MYOCARDIAL RUPTURE	0	0/79 (0.0%)	2	2/222 (0.9%)
	PERICARDITIS	1	1/79 (1.3%)	2	2/222 (0.9%)
	PULMONARY EDEMA	0	0/79 (0.0%)	4	4/222 (1.8%)
	SICK SINUS SYNDROME	0	0/79 (0.0%)	1	1/222 (0.5%)
	VENTRICULAR FIBRILLATION	0	0/79 (0.0%)	3	3/222 (1.4%)
	VENTRICULAR TACHYCARDIA	0	0/79 (0.0%)	3	3/222 (1.4%)
GASTROINTESTINAL DISORDERS		1	1/79 (1.3%)	0	0/222 (0.0%)
	GASTROESOPHOGEAL REFLUX DISEASE	1	1/79 (1.3%)	0	0/222 (0.0%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		2	2/79 (2.5%)	6	5/222 (2.3%)
	ADVERSE DRUG REACTION	0	0/79 (0.0%)	1	1/222 (0.5%)
	CHEST PAIN	2	2/79 (2.5%)	2	2/222 (0.9%)

†Complete or event reported in the interval. Event rate denominators utilize number of subjects with assessment available.

Table 2 (continued). Summary of All Serious Adverse Events within 30 Days

		Randomization Group			
Category	**Adverse Event**	**Control** (N=79)		**AO Therapy** (N=222)	
System Organ Class	**MedDRA PT**	**Events** (n)	**Pts with Events** (n/N; %)	**Events** (n)	**Pts with Events** (n/N; %)
	HYPOTHERMIA	0	0/79 (0.0%)	1	1/222 (0.5%)
	PYREXIA	0	0/79 (0.0%)	2	2/222 (0.9%)
INFECTIONS AND INFESTATIONS		0	0/79 (0.0%)	3	3/222 (1.4%)
	BACTEREMIA	0	0/79 (0.0%)	1	1/222 (0.5%)
	PNEUMONIA	0	0/79 (0.0%)	1	1/222 (0.5%)
	URINARY TRACT INFECTION	0	0/79 (0.0%)	1	1/222 (0.5%)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS		2	2/79 (2.5%)	15	11/222 (5.0%)
	CORONARY ARTERY DISSECTION	0	0/79 (0.0%)	1	1/222 (0.5%)
	DRUG TOXICITY	0	0/79 (0.0%)	1	1/222 (0.5%)
	STENT OCCLUSION	2	2/79 (2.5%)	12	9/222 (4.1%)
	TRAUMATIC HEMATOMA	0	0/79 (0.0%)	1	1/222 (0.5%)
NERVOUS SYSTEM DISORDERS		0	0/79 (0.0%)	2	2/222 (0.9%)
	HYPOXIC ENCEPHALOPATHY	0	0/79 (0.0%)	1	1/222 (0.5%)
	TRANSIENT ISCHEMIC ATTACK	0	0/79 (0.0%)	1	1/222 (0.5%)
PSYCHIATRIC DISORDERS		1	1/79 (1.3%)	1	1/222 (0.5%)
	ANXIETY	1	1/79 (1.3%)	1	1/222 (0.5%)
RENAL AND URINARY DISORDERS		1	1/79 (1.3%)	4	4/222 (1.8%)
	HEMATURIA	0	0/79 (0.0%)	1	1/222 (0.5%)
	RENAL FAILURE ACUTE	1	1/79 (1.3%)	3	3/222 (1.4%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		0	0/79 (0.0%)	2	2/222 (0.9%)
	PNEUMONIA ASPIRATION	0	0/79 (0.0%)	1	1/222 (0.5%)
	RESPIRATORY DISORDER	0	0/79 (0.0%)	1	1/222 (0.5%)
VASCULAR DISORDERS		3	2/79 (2.5%)	14	12/222 (5.4%)
	CAROTID ARTERY STENOSIS	1	1/79 (1.3%)	0	0/222 (0.0%)
	CATHETER SITE HEMATOMA	0	0/79 (0.0%)	3	3/222 (1.4%)
	CATHETER SITE HEMORRHAGE	1	1/79 (1.3%)	1	1/222 (0.5%)
	HEMORRHAGE	0	0/79 (0.0%)	1	1/222 (0.5%)

Table 2 (continued). Summary of All Serious Adverse Events within 30 Days

		Randomization Group			
Category	**Adverse Event**	**Control** (N=79)		**AO Therapy** (N=222)	
System Organ Class	**MedDRA PT**	**Events** (n)	**Pts with Events** (n/N; %)	**Events** (n)	**Pts with Events** (n/N; %)
	HYPOTENSION	0	0/79 (0.0%)	4	3/222 (1.4%)
	RETROPERITONEAL HEMORRHAGE	0	0/79 (0.0%)	1	1/222 (0.5%)
	VASCULAR PSEUDOANEURYSM	1	1/79 (1.3%)	4	4/222 (1.8%)

An overall summary of 30-day adverse events (AEs) is presented in **Table 3**. During the 30-day follow-up period, 118/222 (53.2%) patients in the SSO_2 Therapy group and 37/79 (46.8%) patients in the Control group presented with one or more AEs during study follow-up. SSO_2 Therapy group subjects exhibited a slightly higher incidence of AEs (53.2%) compared to patients randomized to the Control group (46.8%), possibly due to the fact that SSO_2 Therapy subjects received an additional 90 minutes of catheterization time, were administered increased anticoagulation therapy (heparin), and required either a larger single arterial access sheath or a second femoral arterial access site. These factors would be expected to subsequently increase the rates of adverse events.

Table 3. Overall Summary of Adjudicated Adverse Events within 30 Days

	Randomization Group			
	Control (N=79)		**SSO_2 Therapy** (N=222)	
Adverse Event (AE)	**# of Events**	**# (%) of Pts with Events**	**# of Events**	**# (%) of Pts with Events**
Any Adverse Event	58	37 (46.8%)	256	119 (53.6%)
SSO_2 device related AE			0	0 (0%)
SSO_2 procedure related AE			46	40 (18.0%)
Index PCI procedure related AE	16	14 (17.7%)	43	34 (15.3%)
Coronary Artery Disease related AE	23	17 (21.5%)	94	64 (28.8%)
Study Medication related AE	0	0 (0%)	2	2 (0.9%)
Other relationship[1]	18	15 (19.0%)	62	46 (20.7%)
Unknown relationship	1	1 (1.3%)	9	9 (4.1%)
Serious Adverse Event (SAE)	19	15 (19.0%)	89	57 (25.7%)
SSO_2 device related SAE			0	0 (0%)
SSO_2 procedure related SAE			17	14 (6.3%)
Index PCI procedure related SAE	4	4 (5.1%)	17	14 (6.3%)
Coronary Artery Disease related SAE	9	8 (10.1%)	42	32 (14.4%)
Study Medication related SAE	0	0 (0%)	0	0 (0%)
Other relationship[1]	6	5 (6.3%)	10	10 (4.5%)
Unknown relationship	0	0 (0%)	3	3 (1.4%)

Table 3 (continued). Overall Summary of Adjudicated Adverse Events within 30 Days

	Randomization Group			
	Control (N=79)		SSO_2 Therapy (N=222)	
Adverse Event (AE)	**# of Events**	**Adverse Event (AE)**	**# of Events**	**Adverse Event (AE)**
Adverse Event related to AMIHOT II Vessel[2]	8	5 (6.3%)	26	20 (9.0%)

[1]Including pre-existing condition, concurrent condition, concurrent intervention and other relationships

[2]These events include: Control – congestive heart failure (2), stent occlusion (2), cardiogenic shock (1), aortic valve stenosis (1), accelerated idioventricular rhythm (1), and coronary artery disease (1). SSO_2 Therapy – stent occlusion (12), cardiogenic shock (3), myocardial ischemia (2), chest pain (2), cardiac arrest (1), cardiac tamponade (1), coronary artery dissection (1), intracardiac thrombus (1), ventricular fibrillation (1), ventricular tachycardia (1), and hypotension (1).

Due to the SSO_2 Therapy procedure that involved the use of a larger catheter introducer, the necessary use of a second introducer, additional anticoagulation therapy and an incremental period to time for the therapy to be administered, bleeding was an expected adverse event. **Table 4** summarizes bleeding events within 30 days by comparing the two study groups. These events were adjudicated by the Clinical Events Committee and categorized into mild, moderate and severe categories. These categories are defined as follows:

Mild: Bleeding that does not require transfusion or result in hemodynamic compromise

Moderate: Bleeding requiring transfusion that is defined as any blood loss requiring transfusion of blood products

Severe: Intracranial bleeding or bleeding that results in substantial hemodynamic compromise requiring treatment

As shown in **Table 4**, an increase in all bleeding events was observed in the SSO_2 Therapy group as compared to the Control group (24.8% vs. 12.7%). An increase in bleeding events was observed in mild, moderate, and severe bleeding for both access site and non-access site bleeding events.

Table 4. 30-day Bleeding Events by Severity

			Randomization Group			
			Control (N=79)		SSO_2 Therapy (N=222)	
Location	**Bleeding Category**	**Adverse Event**	**# of Events**	**n (%) of Pts with Events**	**# of Events**	**n (%) of Pts with Events**
All Bleeding Events			10	10 (12.7%)	58	55 (24.8%)
All Severe/Life Threatening Bleeding Events			1	1 (1.3%)	3	3 (1.4%)
Access Site			9	9 (11.4%)	41	41 (18.5%)
	Mild	Catheter site hematoma	8	8 (10.1%)	34	34 (15.3%)
	Moderate	Catheter site hematoma	0	0 (0%)	5	5 (2.3%)
		Catheter site hemorrhage	0	0 (0%)	1	1 (0.5%)
	Severe	Catheter site hemorrhage	1	1 (1.3%)	0	0 (0%)
		Retroperitoneal hemorrhage	0	0 (0%)	1	1 (0.5%)
Non-Access Site			1	1 (1.3%)	17	16 (7.2%)

Table 4 (continued). 30-day Bleeding Events by Severity

			Randomization Group			
			Control (N=79)		SSO_2 Therapy (N=222)	
Location	**Bleeding Category**	**Adverse Event**	**# of Events**	**n (%) of Pts with Events**	**# of Events**	**n (%) of Pts with Events**
	Mild	Anemia	0	0 (0%)	6	6 (2.7%)
		Hematuria	0	0 (0%)	1	1 (0.5%)
		Implant site hematoma	0	0 (0%)	1	1 (0.5%)
		Urogenital hemorrhage	0	0 (0%)	1	1 (0.5%)
	Moderate	Anemia	1	1 (1.3%)	1	1 (0.5%)
		Hemorrhage	0	0 (0%)	4	4 (1.8%)
		Traumatic hematoma	0	0 (0%)	1	1 (0.5%)
	Severe	Cardiac tamponade	0	0 (0%)	1	1 (0.5%)
		Hematuria	0	0 (0%)	1	1 (0.5%)
Events Requiring Transfusion			1	1 (1.3%)	14	14 (6.3%)

In summation, SSO_2 Therapy patients had a similar 30-day MACE rate to that observed in Control patients. The incidence rate of both serious adverse events and all adverse events trended higher in the SSO_2 Therapy group, primarily due to the increased incidence of bleeding events, primarily at the catheterization site.

10 Summary of Pre-Clinical Studies

A summary of pre-clinical studies and information for the Downstream AO System, Downstream AO Cartridge, and MI-Cath Infusion Catheter is presented in this section. Results of biocompatibility testing, relevant animal studies of SSO_2 Therapy, engineering testing of the device and components, and software testing are included herein.

10.1 Biocompatibility

The Downstream AO System hardware has no fluid contact or blood contact surfaces. The single use Downstream AO Cartridge, which is loaded into the system, and the intra-coronary MI-Cath Infusion Catheter, have fluid and blood contact.

Biocompatibility tests for the Downstream AO Cartridge and MI-Cath Infusion Catheter were selected in accordance with ISO 10993-1, Biological Evaluation of medical devices – Evaluation and testing, and FDA Blue Book Memorandum #G95-1. Both the AO Cartridge and Infusion Catheter are classified as externally communicating, blood-contacting, short duration devices as defined in ISO 10993-1. All required biocompatibility tests were completed in accordance with the guidelines and were conducted in compliance with Good Laboratory Practices (GLP) as defined in 21CFR§58. The AO Cartridge and Infusion Catheter passed the required biocompatibility testing requirements. Biocompatibility testing results for the cartridge are presented in **Table 5**; testing results for the catheter are presented in **Table 6**.

Table 5. Biocompatibility Testing for the Downstream AO Cartridge

Test Performed / Reference Standard	Extract(s)	Extract conditions / Animal model	Test and Control(s)	Results
Cytotoxicity (Ref: ISO 10993-5)	Minimum Essential Medium (MEM)	120 cm^2 / 20mL37°C – 24 hours Animal model: N/A	Negative control: Polyethylene Positive control: Latex	PASS
Sensitization (Ref: ISO 10993-10)	0.9% NaCl Cottonseed oil (CSO)	120 cm^2 / 20mL 50°C – 72 hours Animal Model: Guinea pig	0.9% NaCl CSO Freund's Complete Adjuvant (CFA)	PASS
Irritation / Intracutaneous Toxicity (Ref: ISO 10993-10)	0.9% NaCl CSO	120 cm^2 / 20mL 50°C – 72 hours Animal Model: Rabbit	0.9% NaCl CSO	PASS
Systemic Toxicity (Ref: ISO 10993-11)	0.9% NaCl CSO	120 cm^2 / 20mL 50°C – 72 hours Animal Model: Mouse	0.9% NaCl CSO	PASS
Ames test (Ref: ISO 10993-3)	0.9% NaCl	120 cm^2 / 20mL 50°C – 72 hours Animal Model: N/A	Sodium Azide Mitomycin-4 4-nitro-0-phenylene-diamine (NPD) aminofluorene (2AF)	PASS
Hemolysis (Ref: BTC protocol No. P0204010*)	0.9% NaCl	120 cm^2 / 20mL 50°C – 72 hours Animal Model: N/A	Negative control: 0.9% NaCl Positive control: Sodium carbonate solution (0.1%)	PASS

* The Biological Test Center (BTC) performs hemolysis testing on device extracts per internal procedures.

Table 6. Biocompatibility Testing for the MI-Cath Infusion Catheter

Test Performed / Reference Standard	Extract(s)	Extract conditions / Animal model	Test and Control(s)	Results
Cytotoxicity (Ref: ISO 10993-5)	Minimum Essential Medium (MEM)	4 grams / 20mL 37°C – 24 hours Animal model: N/A	Negative control: Polyethylene Positive control: Latex	PASS
Sensitization (Ref: ISO 10993-10)	0.9% NaCl Cottonseed oil (CSO)	120 cm^2 / 20mL 50°C – 72 hours Animal Model: Guinea pig	0.9% NaCl CSO Freund's Complete Adjuvant (CFA)	PASS
Irritation / Intracutaneous Toxicity (Ref: ISO10993-10)	0.9% NaCl CSO	4 grams / 20mL 50°C – 72 hours Animal Model: Rabbit	0.9% NaCl CSO	PASS
Systemic toxicity (Ref: ISO10993-11)	0.9% NaCl CSO	4 grams / 20mL 50°C – 72 hours Animal Model: Mouse	0.9% NaCl CSO	PASS
Hemolysis (Ref: BTC protocol no. P0105005*)	0.9% NaCl	120 cm^2 / 20mL 50°C – 72 hours Animal Model: N/A	Negative control: 0.9% NaCl Positive control: Sodium carbonate solution (0.1%)	PASS
Thrombogenicity (Ref: ISO 10993-4)	N/A	6 hour intravascular implant Animal model: Canine	Control article: Tracker®– 38 Infusion Catheter	PASS
Complement Activation (Ref: ISO 10993-4)	Normal Human Serum	6 cm^2 / 1.0mL 37°C – 60 minutes Animal Model: N/A	Positive Control: Cobra Venom Factor Negative Control: High Density Polyethylene Comparison Article: Tracker® – 38 Infusion Catheter	PASS
Ames test (Ref: ISO 10993-3)	0.9% NaCl Dimethyl Sulfoxide (DMSO)	118 cm^2 / 22.6mL 37°C – 72 hours Animal Model: N/A	Sodium Azide Mitomycin-4 4-nitro-0-phenylene-diamine (NPD) 2 aminofluorene (2AF)	PASS

* The Biological Test Center (BTC) performs hemolysis testing on device extracts per their internal procedures.

10.2 Animal Testing

Controlled studies were performed in both porcine and canine AMI models to investigate the safety, effectiveness, and mechanism of action of SSO_2 Therapy[2,3,4,5]. These studies reported improved LV function, infarct size reduction, and a microvascular mechanism of action. The key summary points from animal studies are:

- SSO_2 Therapy administration post- acute AMI suggested improved heart function as measured by left ventricular ejection fraction (LVEF) and regional wall motion score index (RWMSI) as compared with non-treated controls. These animal studies suggested improved LVEF and RWMSI at certain time points.
- SSO_2 Therapy administration post-AMI results in tissue salvage, as determined by post-sacrifice histological measurements of infarct size. Control animals exhibited larger infarcts than SSO_2-treated animals.
- The potential for optimum tissue salvage occurred when 90 minutes of therapy was provided. There was no significant difference when greater than 90 minutes of therapy was given in this animal model, possibly associated with an O_2 toxic effect in animals receiving 180-minute infusions.
- Based on the study protocols utilized, there is limited information available concerning deleterious effects such as end-organ thromboembolism, hemolysis, etc. SSO_2 Therapy was well-tolerated in the AMI models under study.
- SSO_2 Therapy administration post-AMI has exhibited regional myocardial blood flow improvement in treated animals as compared to controls.
- A significant reduction in myeloperoxidase (MPO) levels was observed in SSO_2 -treated animals versus controls; reduced MPO levels indicate improvement in underlying myocardial hypoxia.
- Transmission electron microscopy (TEM) photographs obtained in swine infarct studies suggest amelioration of endothelial cell edema and restoration of capillary patency in ischemic zone cross-sectional histological examination of SSO_2-treated animals as compared to non-treated control animals[6].

The pre-clinical animal studies conducted with SSO_2 Therapy application in AMI models reported acute improvements in cardiac function and metabolic indicators of myocardial health, as well as infarct size reduction, in comparison with non-treated controls. The study limitations include the use of prototype equipment to deliver therapy rather than latest-generation equipment, the lack of concurrent pathology/histopathology to assess tissue and organ-specific safety, and the limited sample sizes employed.

10.3 Engineering/Bench Testing

Verification and Validation (V&V) testing was performed on the component subsystems of the AO System and on the fully integrated device to ensure conformance with requirements. AO System software was developed, documented, and validated in compliance with IEC 60601-1-4 and FDA guidance.

Functional and physical testing was conducted on the single-use AO Cartridge and Infusion Catheter to ensure that these devices met all requirements. The key results of system, cartridge, and catheter V&V testing are presented below.

10.3.1 Downstream AO System Bench Testing

AO System V&V testing was performed on the integrated system and at the subsystem level. The following is a summary of the key test data:

- **General Requirements**

General requirements for medical electrical equipment include safety testing to standards (IEC 60601-1 and IEC 60601-1-2) and confirmation of design control through a review of applicable documentation. System software was developed and controlled using procedures that comply with IEC 60601-1.4.

- **AO Cartridge Subsystem (AOCS) Testing**

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[2] Spears JR *et al.* Hyperoxemic Reperfusion with Aqueous Oxygen Improves Left Ventricular Function and Microvascular Flow in the Postischemic Canine Myocardium. *J Am Coll Cardiol* 1998; 31(2):Abstr Suppl A:449A (1185 – 127).
[3] Spears JR *et al.* Reperfusion Microvascular Ischemia: Attenuation with Aqueous Oxygen. *Circulation* 2000; 102(18): Abstr Suppl II:646(3132).
[4] Spears JR *et al.* Aqueous Oxygen Hyperbaric Reperfusion in a Porcine Model of Myocardial Infarction. *J Invasive Cardiol* 2002; 14(4):160 – 6.
[5] Spears JR *et al.* Aqueous Oxygen Attenuation of Reperfusion Microvascular Ischemia in a Canine Model of Myocardial Infarction. *ASAIO J* 2003; 49(6):716 – 20.
[6] Bartorelli AL. Hyperoxemic Perfusion for Treatment of Reperfusion Microvascular Ischemia in Patients with Myocardial Infarction. *Am J Cardiovasc Drugs* 2003; 3(4):253 –63.

The AOCS interfaces with the AO Cartridge within the AO System housing. AOCS testing was conducted on a stand-alone configuration in a diagnostic (service) mode. This stand-alone subsystem configuration facilitated calibrated measurements of power supply voltages, oxygen supply pressure and temperature through a series of test conditions. When operating the AO Cartridge, the average volume of each piston stroke was 3.05 ml, within specification (2.5 – 3.5 ml). The ability of the AOCS to support SSO_2 delivery above the operational pressure limit of 675 psig was verified. The needle valve actuators were hydrostatically proof-tested at pressures up to 1200 psig. The cartridge housing was proof-tested to 1600 psig. V&V testing demonstrated that the AOCS met all design requirements.

- **Blood Pump Subsystem Testing**

The AO System is equipped with a peristaltic blood pump, ultrasonic flow probe, and flow-feedback controller; together these elements comprise the Blood Pump Subsystem (Blood Pump). The Blood Pump was tested with an AO System configured in a diagnostic (service) mode. Testing was conducted with 5% (w/v) saline solution; this test fluid is a blood analog with respect to the ultrasonic flow probe response. The Blood Pump sustained flow of 75 ml/min at pressures up to the system operating limits. In addition, the Blood Pump controlled flow within 75 ml/min ± 10% over the typical range of return pressure 800 – 1600 mmHg (15.5 – 31.0 psig). V&V testing demonstrated that the Blood Pump met all design requirements.

- **Oxygen Supply Subsystem Testing**

The AO System has an Oxygen Supply Subsystem that regulates the pressure and flow of oxygen gas from the oxygen bottle into the system. The conformance of the required components of this subsystem for oxygen gas handling was verified through testing. The ability of the pressure regulator to control oxygen supply pressure within the specified range (525 – 675 psig) was verified. The set point (800 psig) and service life of the relief valve (100,000 cycles) was verified. V&V testing demonstrated that the Oxygen Supply met all design requirements.

- **Power Supply Subsystem Testing**

V&V testing was conducted on the Power Supply Subsystem of an AO System configured in a diagnostic (service) mode. The conformance of the Power Supply components to system requirements was validated. The AO System power demand was 219 W maximum when charging and 198 W maximum when charged, meeting the requirements. Testing demonstrated that the Power Supply capacity exceeded the 250 W continuous output requirement. The Power Supply batteries provided 106 minutes of operation after being charged for 10 hours (from low battery condition), meeting the requirement of one-hour minimum operation. V&V testing demonstrated that the Power Supply met all design requirements.

- **Integrated AO System Safety Testing**

The AO System is equipped with a hardware Safety Interlock that shuts down system operation safely in the event of an unsafe or out-of-range operating condition. Safety testing was conducted on three AO Systems; each system was tested with an AO Cartridge and a simulated extracorporeal circuit. Twenty-seven safety events were generated according to test protocol. Twenty-four of these events were intended to generate shutdowns, while three events were intended to generate warnings. Examples of these events include out-of-range flow rates, pressures, and presence of air-in-line. For each of the twenty-four shutdown events, the AO System detected the condition and stopped treatment, meeting the requirements. For the three warning events, the AO System generated the appropriate warning as intended. V&V testing demonstrated that the AO System generated the correct safety response as per requirements.

- **Integrated AO System Performance Testing**

Performance V&V testing was performed by conducting simulated SSO_2 Therapy in bench testing. Testing was conducted on three AO Systems configured in normal (clinical) mode consistent with the system's intended use. This testing utilized an *in vitro* clinical simulation of SSO_2 Therapy using slaughterhouse bovine blood (SBB) as the recirculation fluid. Testing required that each AO System control an AO Cartridge to produce hyperoxemic output pO_2 levels between 760 – 1000 mmHg with input SBB conditioned to different pO_2 levels. SBB blood gas samples were taken to establish the three input blood pO_2 ranges: 80 – 90 mmHg, 150 – 200 mmHg, and 250 – 350 mmHg. Test results demonstrated that for all three arterial blood concentration ranges, each of the three AO Systems tested produced a return blood concentration between 760 – 1000 mmHg as required. In addition, the blood flow rate was externally verified during each SSO_2 Therapy simulation. The average blood flow rate for the nine tests was 73.0 ml/min (range 70.0 – 76.5 ml/min). The average SSO_2 solution flow rate was 2.9 ml/min (range 2.8 – 3.0 ml/min). V&V testing demonstrated that the AO System satisfies its essential performance requirements.

10.3.2 Downstream AO Cartridge Bench Testing

The AO Cartridge successfully passed V&V testing for all requirements. Key bench test data are presented in **Table 7** and include results for therapy simulation, blood path (tubing) integrity, proof-pressure testing, hemolysis, and packaging.

Table 7. AO Cartridge Test Results

Test Description	Sample Size	Acceptance Criteria	Data	Result
Performance simulation	N=10	Saline Prep AO Cartridge in < 5 min Deliver pO_2>760 mmHg within 10 min Complete 3 hours of circulation	Prepped in 203 sec 224 sec max 864 mmHg at 10 min 811 mmHg minimum Completed 3 hours (treatment + 90 min)	PASS
Blood Path integrity	N=10	No leakage or failures from testing Priming volume less than 100 ml	No leakage at 60 psig No failures at 3.3 lb Prime volume 60.9 ml (61.6 ml max)	PASS
Test 100 cycles at design pressure	N=10	Perform 100 cycles (deliver 300 ml) at design pressure	All AO Cartridges delivered >300 ml at above 800 psig	PASS
Proof test at 1.5X design pressure	N=10	Five minute proof test, at 1200 psi; no damage to cartridge	All AO Cartridges completed proof testing at 1200 psig	PASS
Blood Hemolysis testing	N=10	3-hour blood test; blood hemolysis less than 20 mg/dL/hr	Hemolysis index 10 mg/dL/hr	PASS
Shelf life testing	N=29	Meets non-destructive and destructive performance tests	3-year real-time aged product satisfied test requirements	PASS
Packaging Testing	N=29	Test per ISTA 1A. Peel test (1 lb min). Leak test per ASTM F2096-01.	All samples passed shipping, peel test and submersion leak test requirements	PASS

10.3.3 MI-Cath Infusion Catheter Bench Testing

The Infusion Catheter successfully passed V&V testing for all requirements. Key bench test data are presented in **Table 8** and include results for therapy simulation, catheter handling properties, leak, proof, tensile, and burst testing, and packaging.

Table 8. Infusion Catheter Test Results

Test Description	Sample Size	Acceptance Criteria	Data	Result
Physical testing	N=30	Measure priming volume Flow test per ISO 10555-3 Annex A	Prime volume 1.60 ml (1.51 – 1.65 ml range); Flow rate per standard is 19.73 ml/min	PASS
Non-destructive performance	N=30	Catheter pushability, stiffness, leak test, proof test at 150 psig	Catheters completed all non-destructive tests without failure	PASS
Destructive performance	N=30	Catheter tensile failure above 2.25 lb Catheter burst failure above 200 psig	Four sections tested per catheter; failure at 3.275 lb minimum Burst test 319.4 psig (278 psig minimum)	PASS
Shelf life testing	N=30	Meets non-destructive and destructive performance tests	3-year accelerated aged product satisfied test requirements	PASS
Packaging Testing	N=30	Test per ISTA 1A. Peel test (1 lb min). Leak test per ASTM F2096-01	All samples passed shipping, peel test and submersion leak test requirements	PASS
Pressure drop and clinical simulation	N=5	Circuit pressure less than 26.9 psig Supports hyperoxemic blood delivery.	Circuit pressure drop 23.4 psig (24.5 psig max) at 75 ml/min; Catheters supported hyperoxemic blood delivery	PASS

10.4 Sterilization

The MI-Cath Infusion Catheter and the Downstream AO Cartridge are ethylene oxide sterilized at a contracted sterilization facility. The sterilization cycle uses an Ethylene Oxide/ Carbon Dioxide gas mixture (8.5% and 91.5% respectively) with a minimum EO gas concentration of 255 mg/l. The nominal gas dwell time is 14.5 hours.

TherOx has validated the sterilization cycle using the "overkill" method outlined in ANSI/AAMI/ISO 11135. The validation consisted of three half-cycles, one fraction cycle, and three full cycles. The validation demonstrated that a sterility assurance level (SAL) of at least 10^{-6} is achieved. The sterilization cycle is re-validated annually.

10.5 Packaging

The MI-Cath Infusion Catheter is inserted into a coiled polypropylene protective tube and placed in a Tyvek/poly pouch. The pouch is heat sealed, labeled, and placed in a unit box. The unit box is labeled and placed in an outer case. The cases are palletized and terminally sterilized with an ethylene oxide sterilant and carbon dioxide gas mixture. The packaged catheter has a three-year shelf life.

The Downstream AO Cartridge is placed in a custom thermoformed tray made of high impact styrene. A clear PETG lid snaps into the tray, keeping the AO Cartridge securely in place. The lid is well vented and does not interfere with the EO sterilization process. The tray is then placed in a Tyvek/poly pouch. The pouch is heat sealed, labeled, and placed in a unit box. The unit box is labeled and placed in an outer case. The cases are palletized and terminally sterilized with an ethylene oxide sterilant and carbon dioxide gas mixture. The packaged AO Cartridge has a three-year shelf life.

11 Summary of Clinical Studies

11.1 Early Feasibility Studies

Phase I/IA

The first human study of SSO_2 Therapy in AMI was an IDE-sanctioned Phase I pilot study conducted in the U.S. and Italy beginning in 1999, involving 29 anterior AMI subjects[7]. This study was conducted in two separate phases: Phase I involved 9 subjects who received SSO_2 Therapy selectively, with the hyperoxemic reperfusion provided through a guiding catheter in the left main coronary ostium at a flow rate of 100 ml/min. In Phase IA involving 20 subjects, the reperfusion was provided sub-selectively in the infarct-related artery through an infusion catheter at a flow rate of 75 ml/min. To assess ventricular function, left ventriculography was performed pre- and post-SSO_2 infusion, and regional wall motion was assessed pre-SSO_2 Therapy, during SSO_2 infusion, and at 24-hours, 1 and 3-months post-SSO_2 Therapy. SSO_2 was infused successfully in all cases. No adverse events were documented that were related to the Downstream AO System or required accessories, or to SSO_2 Therapy administration.

Results of the Phase I/IA studies showed LV functional improvements post-AMI; mean ejection fraction (EF) improved from 48.6% to 56.0% over three months ($p<0.001$). In addition, wall motion score index, a measure of ventricular contractility, improved significantly over three months as well. The analysis showed that these improvements in global LV functional measures were due to recovery of ventricular function in the infarct zone; regional WMSI assessments showed no change in the non-infarct zone[8,9]. These results pointed to strong functional improvements in the heart after SSO_2 Therapy administration, with no documented adverse events that were related to the Downstream System or accessories. Results from the Phase I/IA study fixed the infusion flow rate and sub-selective delivery and served as a basis for additional clinical trials.

OYSTER-AMI Study

The clinical use of the current-generation Downstream AO System for administration of SSO_2 Therapy was examined first in the Supersaturated Oxygen in ST-Elevation Reperfused-AMI, or OYSTER-AMI study conducted on anterior STEMI patients by Dr. Antonio Bartorelli in Milan, Italy. OYSTER-AMI examined the safety and effectiveness of SSO_2 Therapy in a 41-patient study (21 SSO_2 Therapy subjects, 20 matched-control subjects).

The non-randomized study evaluated both SSO_2 Therapy patients and a control population of case-matched subjects. Ninety (90) minutes of SSO_2 infusion was performed with hyperoxemic blood reperfusion provided via sub-selective infusion catheter into the infarct-related artery post-PCI with stent placement. Cardiac enzyme data were evaluated as an indirect measure of the extent of infarction, and LV functional recovery was evaluated by serial 2-D contrast echocardiography at six time points: immediately post-PCI (baseline), and at 24 hrs, 7 days, 1 month, 3 months, and 6 months post-procedure in both groups. LVEF and wall motion score index (16-segment model) were evaluated at each of these time points. A total of 41 subjects were examined in the OYSTER-AMI study, including 21 SSO_2 Therapy patients and 20 Control patients.

Results for Cardiac enzyme data showed a significant decrease in the time to peak creatine kinase (CK), measured from time from symptom onset (SSO_2 Therapy = 9.4 ± 3.4 hrs vs. Control = 14.2 ± 5.3 hrs; $p < 0.001$). The difference in CK half-life was significant as well: SSO_2 Therapy = 23.4 ± 8.9 hrs vs. Control = 30.5 ± 5.8 hrs ($p<0.01$). These decreases observed in the SSO_2 Therapy group translate into less total CK enzyme release. These results were accompanied by functional recovery, as seen in

[7] Dixon SR *et al.* Initial Experience with Hyperoxemic Reperfusion after Primary Angioplasty for Acute Myocardial Infarction. *J Am Coll Cardiol* 2002; 39(3):387-92.
[8] Dixon SR *et al.* Early recovery of infarct zone function with hyperoxemic reperfusion after primary percutaneous transluminal coronary angioplasty. *Am J Cardiol* 2000; 86 (Suppl. 8A): 8i.
[9] Dixon SR *et al.* Global and regional left ventricular function after intracoronary hyperoxemic perfusion with the Aqueous Oxygen system in acute myocardial infarction: TherOx study. *Circulation* 2000; 102 (Suppl.): II-386.

LVEF and wall motion score index measurements. For SSO_2 subjects, the six-month relative improvement in LVEF was 28%; in contrast, the Control group only improved by 2.5% ($p<0.01$). Similarly, relative improvements in wall motion score index from baseline to six months were 26% in the SSO_2 Therapy group as compared to 2.4% in the Control group.

The improvements in LV functional recovery, ST elevation recovery, and reduction in cardiac enzyme release observed in OYSTER-AMI suggested that SSO_2 Therapy potentially could be used effectively in a STEMI population.

11.2 AMIHOT I Clinical Trial

11.2.1 Background

The AMIHOT I study examined the safety and effectiveness of SSO_2 Therapy in both anterior and inferior STEMI patients undergoing successful reperfusion therapy via PCI up to 24 hours from symptom onset; 289 patients were enrolled in 23 investigational sites. This Phase II study, termed the Acute Myocardial Infarction with HyperOxemic Therapy, or AMIHOT I trial, was conducted from January 16, 2002 to April 3, 2004.

11.2.2 Study Design and Methods

Study Design
The AMIHOT I study objective was to determine whether the adjunctive administration of SSO_2 Therapy after PCI and stenting in a group of patients presenting less than or equal to ($\leq$) 24 hours from AMI symptom onset improves left ventricular function and reduces the area of infarction, with no increased incidence of 30-day Major Adverse Cardiac Events (MACE) when compared to a Control group receiving PCI with stenting alone. The AMIHOT I clinical trial was prospectively designed as a randomized (1:1), controlled, multicenter trial.

The AMIHOT I study design included three co-primary effectiveness endpoints to be evaluated by test of superiority:

- 5% reduction in infarct size as measured by the percent of left ventricular volume, assessed by Tc-99m Sestamibi SPECT imaging at 14 (±7) days post PTCA/stent placement.
- 0.2 unit increase in regional wall motion score index (WMSI) in the infarct zone over three months (90 ± 7 days) as evidence of left ventricular function recovery.
- ST-segment recovery as evidenced by a 50% lower ST-deviation vs. time trend curve area in the SSO_2 treatment group during the first three hours of continuous monitoring as an indicator of myocardial ischemia reversal.

The primary safety endpoint was based on the number of patients experiencing Major Adverse Cardiac Events (MACE), comprising the total incidences of death, reinfarction, target vessel revascularization, and stroke within one month (30 days) of enrollment.

Methods
Key AMIHOT I selection criteria considered patients who were diagnosed with acute myocardial infarction (AMI) and admitted to the hospital within 24 hours of symptom onset. Qualifying AMIs met specific electrocardiographic and angiographic criteria prior to randomization, including a > 1 mm ST-segment elevation as measured by ECG, and a pre-PCI/stenting angiographic TIMI score of 0, I, or II in the cardiac catheterization laboratory. Successful revascularization with PCI was required for AMIHOT I subjects, as measured by a post-procedure TIMI score ≥ II. SSO_2 Therapy patients received an intracoronary 90-minute infusion of hyperoxemic blood post-PCI via infusion catheter.

11.2.3 Results and Conclusions

Two hundred sixty-nine (269) patients were randomized into the AMIHOT I trial, including 135 Control subjects and 134 SSO_2 Therapy subjects. A comparison of baseline demographic and clinical patient characteristics between the two randomized groups reveals no statistically significant differences that would indicate a bias in the clinical outcome for these patients.

Results for the Control/SSO_2 Therapy group comparisons for the three co-primary effectiveness endpoints demonstrated a nominal improvement in the test group; this nominal improvement did not achieve clinical and statistical significance in the entire population. However, a post hoc analysis of SSO_2 Therapy patients who were revascularized within 6 hours of AMI symptom onset and who had anterior wall infarction showed a marked improvement in all three co-primary endpoints as compared to Controls.

Infarct size results are expressed as a percentage of the left ventricle. This endpoint was established on the basis of numerous peer-reviewed publications of this biomarker that demonstrate a 5% median infarct size reduction is clinically meaningful. The use of the median in the evaluation of this endpoint is predicated on the obvious skewness (particularly due to the number of zeros) of the data distribution typically seen in infarct size studies. The all-patient < 24-hour group showed a 2% absolute reduction in median infarct size, from 13% for Control subjects to 11% in the SSO_2 Therapy group (Wilcoxon rank-sum test; one-sided p-value = 0.3). The infarct size reduction for anterior STEMI subjects treated within 6 hours of symptom onset showed that SSO_2 Therapy subjects exhibited a 14% absolute reduction in median infarct size from 23% in the Control group to 9% in the SSO_2 Therapy group (Wilcoxon rank-sum test; one-sided p-value = 0.04). Expressed in terms of mean data, infarct size was reduced from 17.4% in the Control group to 16.9% in the SSO_2 Therapy group for the entire study cohort, a mean reduction of 0.5%, but this statistic is less meaningful in light of the right-skewed frequency distribution involved. In the anterior < 6 hr cohort, mean infarct size was reduced in this patient subgroup from 23.0% in the Control group to 17.3% in the SSO_2 Therapy group, a mean reduction of 5.7%.

Effectiveness results for the other two co-primary endpoints (regional wall motion score index improvement, ST area reduction) in the AMIHOT I trial were consistent with the infarct size data. The results for regional wall motion score index improvement (decrease) at 3 months (90 days), as compared to baseline, demonstrated a nominal improvement in all patients in the SSO_2 group as compared to Controls (-0.62 vs. –0.57, respectively, ANCOVA one-sided p-value = 0.24); the results were statistically significant when only the anterior $\leq$ 6 hr population was examined (-0.75 vs. –0.54 for SSO_2 and Controls, ANCOVA one-sided p-value =0.03). As seen in the infarct size measurements, the observed improvement in SSO_2 Therapy subjects versus Controls is greatest in the $\leq$ 6 hr anterior patient population.

ST-segment area reduction is believed to represent the continuing ischemic burden on the heart in the post-acute phase for AMI patients. Results for this biomarker obtained at 3 hours post-PCI were consistent with both infarct size and wall motion data; results were comparable for all patients studied (median ST area = 0 μV-min for both groups, Wilcoxon rank-sum test one-sided p-value = 0.5) and significantly better in the anterior $\leq$ 6 hr patient group (median areas = 0 vs. 311 μV-min for SSO_2 and Controls, Wilcoxon rank-sum test one-sided p-value = 0.01).

Key safety data revealed no statistically significant differences in the composite primary endpoint of one-month (30 days) Major Adverse Cardiac Event (MACE) rates between the SSO_2 Therapy and Control groups. The 30-day MACE results are presented in **Table 9**. MACE includes the combined incidence of death, reinfarction, target vessel revascularization, and stroke. In total, 9/134 (6.7%) subjects in the SSO_2 Therapy group and 7/135 (5.2%) subjects in the Control group experienced 30-day MACE. The slightly higher 30-day MACE rate observed in SSO_2 Therapy subjects was not statistically significant (p-value = 0.02 when evaluating the non-inferiority test of the null hypothesis that SSO_2 Therapy MACE rate is at least 8% [absolute] higher than the Control group MACE rate).

Table 9. AMIHOT I Primary Safety Endpoint Evaluation (30-Day MACE)

	Randomization Group			
	Control (N=135)		**SSO_2 Therapy** (N=134)	
Adverse Event	**Events**† (n)	**Pts with Events** (n/N; %)	**Events**† (n)	**Pts with Events** (n/N; %)
Composite 30-Day MACE*	10	7/135 (5.2%)	11	9/134 (6.7%)
Death		2/135 (1.5%)		4/134 (3.0%)
Target Vessel Revascularization‡		3/135 (2.2%)		3/134 (2.2%)
Reinfarction		3/135 (2.2%)		3/134 (2.2%)
Stroke		2/135 (1.5%)		1/134 (0.7%)

†Event count: count of number of unique event types experienced per patient
‡AMIHOT main vessel or branches
*p-value = 0.02 (Unconditional Test of Non-Inferiority using difference of two Binomial Proportions)

In summary, although a slight trend was observed for SSO_2 Therapy patients as compared to Control subjects, the results for the entire AMIHOT I population did not achieve the requisite level of statistical significance for the three co-primary effectiveness endpoints. However, post hoc analysis of the anterior AMI $\leq$ 6 hr patient cohort suggested the potential for therapeutic effectiveness in this subgroup, with improvements noted for all three effectiveness endpoints. These effectiveness results, coupled with a comparable 30-day MACE safety profile between the SSO_2 Therapy and Control groups, formed the basis of the pivotal AMIHOT II trial to confirm the validity of the AMIHOT I findings for anterior AMI $\leq$ 6 hr patients.

11.3 AMIHOT II Clinical Trial – Pivotal study for PMA application

11.3.1 Background

The AMIHOT II trial was designed to test the superiority of SSO_2 Therapy in reducing infarct size in anterior AMI patients treated within six hours of symptom onset, with safety evaluation by comparing the incidence of 30-day MACE between SSO_2 Therapy and Control groups. The promising results observed in this anterior < 6 hr AMI patient population in the AMIHOT I study served as the basis for selecting this cohort in the AMIHOT II trial.

11.3.2 Study Design and Methods

Objective
To determine whether intracoronary perfusion of hyperoxemic blood in the SSO_2 Therapy group immediately after successful PCI/stenting within 6 hours of symptom onset for the treatment of anterior acute myocardial infarction reduces the area of infarction (% left ventricle) as measured by Tc-99m Sestamibi SPECT imaging at 14 days post-PCI, with no worse than a 6% (absolute) increase in the incidence of Major Adverse Cardiac Events (MACE), comprising the combined incidence of death, re-infarction, target vessel revascularization, and stroke at the latter of either 30 days post-PCI or hospital discharge, when compared to a Control group receiving PCI/stenting alone.

Primary Effectiveness Endpoint
Reduction in infarct size as measured by percent of left ventricular volume, assessed by
Tc-99m Sestamibi SPECT imaging at 14 days post PCI/stenting, as an indicator of treatment effectiveness by a hypothesis test of superiority.

Primary Safety Endpoint
A composite safety endpoint based on the incidence of death, reinfarction, target vessel revascularization, and stroke occurring less than or equal to one month (30 days) after enrollment or until hospital discharge, whichever is later. The composite safety endpoint was evaluated by a test of non-inferiority within a safety delta less than or equal to 6.0%. In addition, all Serious Adverse Events, whether they are determined to be device-related or not, were investigated and reported as part of the overall evaluation of device safety.

Endpoint Evaluation
Infarct size was measured by Tc-99 sestamibi SPECT imaging at 14 (± 7) days by the independent SPECT core laboratory at the Mayo Clinic (Rochester, MN). In addition, SSO_2 Therapy was required to show non-inferiority in the incidence of 30-day Major Adverse Cardiac Events (MACE) within a 6.0% safety delta. MACE is a composite endpoint that includes the combined incidence of death, re-infarction, target vessel revascularization, and stroke. Primary safety endpoint adjudication was performed by the independent Clinical Events Committee (CEC).

The AMIHOT II trial had a Bayesian statistical design that allows for the proportional borrowing of data from the previously completed AMIHOT I trial. The Bayesian statistical model was pre-specified; the model required that the posterior probability for success to be greater than 95.0% for both the efficacy and safety endpoints. An unbalanced randomization ration of 2.8:1 (SSO_2 Therapy: Control) was utilized to satisfy acceptable power requirements.

Methods
Key AMIHOT II selection criteria considered patients who were diagnosed with anterior acute myocardial infarction (AMI) and revascularized via PCI in the cath lab within 6 hours of symptom onset. Qualifying AMIs met specific electrocardiographic and angiographic criteria prior to randomization, including a > 1 mm ST-segment elevation as measured by ECG, and a pre-PCI/stenting angiographic TIMI score of 0, I, or II in the cardiac catheterization laboratory. Successful revascularization with PCI was required for AMIHOT II subjects, as measured by a post-procedure TIMI score ≥ II. After patients were determined to meet angiographic criteria, randomization was performed via telephone using an automated procedure. Patients assigned to SSO_2 Therapy received an intracoronary 90-minute infusion of hyperoxemic blood post-PCI via infusion catheter.

Arterial blood gas (ABG) readings were taken before and during SSO_2 Therapy administration in order to ensure adequate blood oxygenation for the procedure. Routine physiological parameters including blood pressure, ACT levels, and heart rate and rhythm measurements were taken immediately after completion of PCI for all patients and at 30, 60, and 90 minutes during SSO_2 infusion for the SSO_2 Therapy group. Additional blood samples were drawn at 8, 16 and 24 hours post-PCI in both study groups; cardiac enzyme levels and diagnostic information were collected from these samples.

11.3.3 Independent Study Committees

Clinical Events Committee (CEC) and Data Safety Monitoring Board (DSMB)
The AMIHOT II Clinical Events Committee (CEC) was responsible for comprehensive adverse event adjudication on an ongoing basis throughout the study. CEC membership was comprised of three (3) interventional cardiologists who did not participate in the study.

A Data Safety Monitoring Board (DSMB) was utilized for safety monitoring in this trial. No formal statistical rule for stopping the trial was defined, but comprehensive review of adjudicated adverse event reporting was performed during the study to ensure that trial subjects were not exposed to unforeseen risk. DSMB membership consisted of five independent experts, including three (3) interventional cardiologists, one (1) non-interventional cardiologist and one (1) biostatistician.

11.3.4 Results and Conclusions

A total of 317 patients were enrolled in the AMIHOT II trial, including 13 run-in (training) patients and 304 randomized patients (222 SSO_2, 79 Control, and 3 randomized in error). The study enrollment was conducted from September 13, 2005, the date of the first patient enrollment, to June 28, 2007, the date of completion for the last 30-day patient follow up.

Patient Baseline Characteristics
A review of baseline patient information demonstrates comparability between the SSO_2 and Control study groups. **Tables 10** and **11**, shown below, display median data for baseline patient characteristics and cath lab procedural results. Angiographic data were evaluated by an independent core laboratory, the Cardiology Research Foundation (CRF).

Table 10. AMIHOT II Baseline Patient Characteristics

	Control Group (N=79)	**SSO_2 Therapy Group (N=222)**
Age (years)	59	60
Male	87.3%	77.9%
Diabetes	13.9%	16.2%
Hypertension	45.6%	46.9%
Hyperlipidemia	43.0%	45.1%
Current Smoking	43.0%	38.3%
Prior Myocardial Infarction	8.9%	9.0%
Prior PCI of target vessel	10.1%	5.9%

Table 11. AMIHOT II Cardiac Catheterization Laboratory Procedural Results (pre-randomization)

	Control Group (N=79)	**SSO_2 Therapy Group (N=222)**
Time intervals (min):		
Symptom Onset to ER arrival	90	110
Door to Balloon	75	77
Symptom Onset to reperfusion	171	195
Infarct lesion location:		
Proximal LAD†	46.8%	47.7%
Mid LAD	51.9%	49.1%
Distal LAD	0.0%	2.3%
Diagonal branch of LAD	1.3%	0.9%
LVEF %	40	40
Stent implanted	97.5%	99.1%
Glycoprotein IIb/IIIa inhibitor use	64.6%	68.0%
Rescue PCI (failed thrombolytics)	8.9%	5.0%

Table 11 (continued). AMIHOT II Cardiac Catheterization Laboratory Procedural Results (pre-randomization)

TIMI flow pre-PCI:‡		
0/1	69.9%	75.5%
2	13.7%	17.1%
3	16.4%	7.4%*
TIMI flow post-PCI: ‡		
0/1	2.8%	1.4%
2	4.2%	10.2%
3	93.0%	88.4%

†LAD = left anterior descending coronary artery
‡as determined by independent angiographic core laboratory

Table 11 shows that the study groups are well matched in terms of cath lab procedural characteristics as well. As shown in the table, median time interval data for door-to-balloon, symptom onset to emergency room arrival, and symptom onset to reperfusion times are slightly longer for the SSO_2 Therapy group. Other procedural characteristics, including infarct lesion location, baseline left ventricular ejection fraction (LVEF), and stent implantation were comparable. The incidence of rescue PCI cases was nominally higher in the Control group.

Pre-PCI TIMI flow in the infarct vessel was nominally better in the Control group. Post-PCI TIMI flow was also nominally better in the Control group.

Endpoint Results

Effectiveness

The primary effectiveness endpoint of the study required finding evidence of superiority of infarct size reduction with SSO_2 Therapy, as compared to patients receiving PCI with stenting alone. The surrogate endpoint established for this study was infarct size measurement by Tc-99 sestamibi SPECT imaging at 14 (±7) days post-procedure. This endpoint was established on the basis of numerous peer-reviewed publications of this biomarker that indicate a 5% median infarct size reduction is clinically meaningful. The use of the median in the evaluation of this endpoint is predicated on the obvious skewness (particularly due to the number of zeros) of the data distribution typically seen in infarct size studies. The study population included qualified subjects who experienced anterior acute myocardial infarction revascularized by means of PCI with stenting within 6 hours of symptom onset. The AMIHOT II study results demonstrated effectiveness of SSO_2 Therapy in reducing median infarct size from 26.5% of the left ventricle in the Control group to 20.0% in the SSO_2 Therapy group in the AMIHOT II study, an absolute median reduction of 6.5%. Alternatively, mean infarct size was reduced from 27.1% in the Control group to 23.2% in the SSO_2 Therapy group, a mean reduction of 3.9%, but this statistic is less meaningful in light of the right-skewed frequency distribution involved.

A pre-specified hierarchical Bayesian model was used to evaluate the infarct size data for group differences. To account for the skewness of the data, a log-transformed scale was used. Differences of means on the log-transformed scale correspond roughly to differences in median on the original scale; this correspondence is exact if the log-transformed data are truly normally distributed. The model considered all AMIHOT I infarct size data, modeled in four categories: anterior/non-anterior wall infarction and time to reperfusion less than or equal to, or greater than, 6 hours. The model allowed for a flexible amount of pooling of the AMIHOT I infarct size data, with a greater degree of pooling if the AMIHOT II study results were consistent with those observed in AMIHOT I. Using this model, the Bayesian posterior probability of superiority for SSO_2 Therapy was 96.9%, thus satisfying the pre-established efficacy endpoint.

The secondary effectiveness marker of the study was ST-segment elevation measured in the first 3 hours post-PCI by area under the curve, using continuous ECG recording. At 3 hours post-PCI, a total of 48/75 (64.0%) Control subjects and 121/202 (59.9%) SSO_2 Therapy subjects had ST area = 0, which can be interpreted as no continuing ischemia.

Safety

The primary safety endpoint for the AMIHOT II trial required a determination of non-inferiority in the 30-day MACE rate, comparing the SSO_2 Therapy group with the Control group, using a one-sided safety delta of 6.0%. Endpoint evaluation was performed using a Bayesian hierarchical model that factored in the 30-day MACE data from both the AMIHOT I and II studies. Study results demonstrated that the primary safety endpoint was achieved successfully, with observed 30-day MACE rates of 3.8% in the Control group and 5.4% in the SSO_2 group in the AMIHOT II trial. The posterior probability of an increase of less than 6% in 30-day MACE rate was 99.5%, successfully achieving the study endpoint. **Table 12** displays the 30-day MACE individual component rate data for the study. As shown in the table, trends in slightly higher 30-day mortality and MACE were noted in the SSO_2 Therapy group as compared to Controls.

Table 12. AMIHOT II 30-Day MACE Rates

	Randomization Group			
	Control (N=79)		SSO_2 Therapy (N=222)	
Adverse Event	**Events (n)**	**Pts with Events n (%)**	**Events (n)**	**Pts with Events n (%)**
30-day MACE assessment available		79/79 (100.0%)		222/222 (100.0%)
Composite 30-Day MACE	5	3/79 (3.8%)	19	12/222 (5.4%)
Death	0	0/79 (0%)	4	4/222 (1.8%)
Target Vessel Revascularization[1]	3	3/79 (3.8%)	9	8/222 (3.6%)
Reinfarction	2	2/79 (2.5%)	6	4/222 (1.8%)
Stroke	0	0/79 (0.0%)	0	0/222 (0.0%)

[1]LAD target vessel or branches

In terms of non-MACE adverse events observed within 30 days, a trend in access site-related and non-access site related bleeding was observed in the SSO_2 Therapy group, most likely caused by the extended patient time in the cath lab and the continuing administration of anticoagulant therapy. These trends did not result in significant differences in transfusions or other serious complications. SSO_2 Therapy may be associated with an increased risk of minor bleeding events.

Additional safety data for the AMIHOT II study were collected through 12 months post-procedure. Data for 12-month MACE results are displayed in **Table 13**. As seen in the table, 12-month MACE rates were comparable between the two groups, with a slightly higher observed rate in the SSO_2 Therapy group (12.7% vs. 10.4%). Patient mortality at 12 months was slightly higher in the SSO_2 Therapy group (3.6% vs. 1.3%), while rates of TVR and reinfarction at 12 months were comparable between the groups (9.1% and 3.9% vs. 8.6% and 4.1%).

Table 13. AMIHOT II 12-Month MACE Rates

	Randomization Group			
	Control (N=79)		SSO_2 Therapy (N=222)	
Adverse Event	**Events (n)**	**Pts with Events n (%)**	**Events (n)**	**Pts with Events n (%)**
12-month MACE assessment available		77/79 (97.5%)		220/222 (99.1%)
Composite 12-month MACE	11	8/77 (10.4%)	47	28/220 (12.7%)
Death	1	1/77 (1.3%)	8	8/220 (3.6%)
Target Vessel Revascularization[1]	7	7/77 (9.1%)	25	19/220 (8.6%)
Reinfarction	3	3/77 (3.9%)	13	9/220 (4.1%)
Stroke	0	0/77 (0.0%)	1	1/220 (0.5%)

[1]LAD target vessel or branches

Conclusions

The AMIHOT II study was a prospective, randomized evaluation of the safety and effectiveness of the adjunctive use of SSO_2 Therapy administered to anterior acute myocardial infarction patients revascularized by means of PCI with stenting within six hours of symptom onset. SSO_2 Therapy subjects were compared to a randomized Control group receiving only the standard of care. The results of this study indicate that SSO_2 Therapy is effective in reducing infarct size and is safe when used in accordance with its recommended instructions for use.

12 Panel Recommendation

TBD

13 CDRH Decision

FDA issued an approval order on [date]. The conditions of approval include: TBD.

14 Approval Specifications

Instructions for Use: See Labeling
Post-Approval Requirements and Restrictions: See Approval Order.