TherOx DownStream System
Instructions for Use

DownStream® System DS-1
DownStream® Cartridge DSC-2
SSO_2 Catheter

Caution: Federal (USA) law restricts this device to sale by or on the order of a physician.

- Read all instructions and warnings prior to use.
- The DownStream® System may be used only by trained personnel under the supervision of physicians trained in angiography and percutaneous coronary intervention (PCI).
- Do not resterilize or reuse the DownStream® Cartridge, SSO_2 Catheter, or disposable accessories; these devices are for single use only.
- Only TherOx personnel or authorized representatives may ship, install and service the DownStream System.

Indications for Use

The TherOx DownStream System is indicated for the preparation and delivery of SuperSaturated Oxygen Therapy (SSO_2 Therapy) to targeted ischemic regions perfused by the patient's left anterior descending coronary artery 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 caused by a left anterior descending artery infarct lesion.

Contraindications

- Ipsilateral insertion of a second sheath in a single femoral artery for SuperSaturated Oxygen Therapy is strictly contraindicated.
- Presence of an intra-aortic balloon pump.
- Proximal coronary stenosis that restricts flow with the SSO_2 Catheter in place.
- Presence of a post-intervention non-stented coronary dissection or perforation.
- Cardiac valvular stenosis or insufficiency, pericardial disease or non-ischemic cardiomyopathy.
- Pregnant or nursing women.
- Cardiogenic shock.
- Patients contraindicated for anticoagulation therapy.
- Subjects with ventricular pseudoaneurysm, VSD, or severe mitral valve regurgitation (with or without papillary muscle rupture).
- Hemoglobin < 10 g/dL.
- Gastrointestinal or genitourinary bleeding within the last two months, or any major surgery (including CABG) within six weeks of procedure.

Summary of Warnings

- Only physicians who have received appropriate training in the use of the DownStream System should perform SuperSaturated Oxygen Therapy (SSO_2 Therapy).
- SuperSaturated Oxygen Therapy must be performed in the cardiac catheterization laboratory (cath lab). The patient must not be moved while the catheter is in place.
- Under no circumstances should the extracorporeal circuit be disconnected and restarted outside the cath lab.

- Do not use any type of catheter for SSO_2 Therapy other than the SSO_2 Catheter. Inspect the SSO_2 Catheter and packaging for damage and kinking prior to use; do not use if the catheter or packaging is damaged.
- The DownStream 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 cartridge and packaging for damage prior to use; do not use if the cartridge or packaging is damaged.
- Use only 0.9% Normal saline (Isotonic solution).
- Verify that all connections are secure and tight prior to initiating prime.
- Verify that the return line of the cartridge is not connected to the SSO_2 Catheter prior to initiating prime.
- The bubble detector is disabled during prime. Ensure that return line is fully blood primed with no presence of air or bubbles in the line prior to making wet-to-wet connection to the SSO_2 Catheter.
- Do not disconnect return line from SSO_2 Catheter or draw line from sheath when therapy is in progress. Procedure must be stopped before disconnection.
- Do not exceed the SSO_2 Therapy duration of 60 minutes.
- Do not re-use the single-use cartridge and SSO_2 Catheter. Re-use of the cartridge and SSO_2 Catheter may result in patient infection. In addition, the cartridge is programmed for single use only and attempted re-use will result in failure to provide treatment.
- Dispose of used cartridges and SSO_2 Catheters using standard hospital procedures to eliminate hazardous waste.
- Only qualified personnel trained in oxygen safety and handling should change the oxygen bottle.
- To avoid risk of electric shock, this equipment must only be connected to a supply mains with protective earth.
- No modification of this equipment is allowed.

Summary of Precautions

- The index PCI procedure may be done using femoral or radial access; the SSO_2 Therapy blood draw requires a femoral arterial access site.
- If the recommended 7F Merit Medical Custom Sheath Introducer is not used, or less than an 8F introducer sheath (coaxial approach) or 5F introducer sheath (dual site approach) is used for femoral access, SSO_2 Therapy may stop due to inadequate flow rate.
- Do not use the system if the oxygen bottle pressure is less than 800 psig (54.4 bar).
- Do not expose electrical connections, including the transducer port, to fluid contact.
- Do not stretch the return line while loading into the flow probe.
- Ensure that the return line is fully seated in the flow probe slot before latching to prevent the flow probe door from pinching the line.
- Ensure fluoroscopic contrast agents delivered through the SSO_2 Catheter have been flushed prior to priming circuit; these viscous solutions may result in a flow stoppage after connection to the cartridge return line is made.
- Ensure that draw and return lines are not kinked or restricted prior to starting prime or at any other time during use.
- Do not unplug the transducer once the cartridge has been prepped.
- After placement, inspect the SSO_2 Catheter under fluoroscopic visualization to ensure that it is seated correctly in the LMCA and does not restrict blood flow.
- If the SYSTEM BATTERY POWER LOW message is displayed, plug the system into an electrical outlet.
- Position the system as necessary to provide access to the AC power cable and the Potential Equalization Terminal located on the instrument's back panel. Potential equalization can be managed in accordance with IEC 60601-1.

Potential Adverse Events

Potential adverse events include risks associated with interventional cardiology procedures. Complications from these events may necessitate emergency CABG or intra-aortic balloon pump placement, or recatheterization.

- Death
- Acute Myocardial Infarction (AMI)
- Stent Thrombosis
- Revascularization (CABG or PCI)
- Congestive Heart Failure

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

Device Description

SuperSaturated Oxygen (SSO_2) Therapy is an adjunctive cardiac catheterization laboratory initiated procedure targeted at the left main coronary artery (LMCA) of an acute myocardial infarction (AMI) patient after successful percutaneous intervention (PCI) with stenting has been performed of the left anterior descending coronary artery. The equipment necessary for SSO_2 Therapy is comprised of three components: the DownStream® System ("system"), the DownStream® Cartridge ("cartridge"), and the SSO_2 Catheter. The system and cartridge function together to create a highly oxygen-enriched saline solution called SuperSaturated Oxygen ("SSO_2") solution. A small amount of autologous blood is mixed with the SSO_2 solution producing oxygen-enriched hyperoxemic blood which is then delivered to the targeted major epicardial artery via the SSO_2 Catheter. The duration of SSO_2 Therapy is 60 minutes.

DownStream System

The system is the electromechanical device (console) that controls the cartridge and monitors performance and safety during administration of SSO_2 Therapy. The system has safety features that continuously monitor system parameters such as the blood flow rate and pressure and detect potentially unsafe conditions such as the presence of air-in-line. A display screen guides the health care professional through setup and clinical operation. The system is non-sterile and has no direct contact with the patient or the blood flow path. The system is intended to be mains-operated (AC-powered) and stationary during use but is equipped with battery backup power. The system is designed for operation in a cardiac catheterization laboratory and must be operated and monitored by trained personnel when providing SSO_2 Therapy.

DownStream Cartridge

The cartridge is a single-use disposable device that is loaded into the system by a trained healthcare professional. The cartridge has a three-chambered body that creates SSO_2 solution from inputs of hospital-supplied oxygen and physiologic saline and mixes the SSO_2 solution with arterial blood within the cartridge blood path. The cartridge has a tube set that draws the patient's arterial blood through the draw line and returns oxygen-enriched hyperoxemic blood through the return line to the SSO_2 Catheter. The cartridge draw line connects to an arterial sheath. Sheath placement may be coaxial (single arterial access site) or contralateral (two arterial access sites) at the physician's discretion. A physician makes two line connections during the initiation of SSO_2 Therapy: the cartridge draw line is attached to the arterial sheath before priming the blood flow path, and the return line is attached to the SSO_2 Catheter after the blood flow path is successfully primed. The priming volume of the cartridge is approximately 60 ml.

SSO_2 Catheter

The SSO_2 Catheter is a 5F (O.D.) over-the-wire catheter that is equipped with a standard luer fitting at the proximal end for attachment to the return line of the cartridge. The SSO_2 Catheter has a length of 100 cm and is shaped to facilitate placement in the left main coronary ostium using the PCI arterial access site. The SSO_2 Catheter is placed in the ostium of the LMCA using a guidewire by the trained physician and is connected to the cartridge after blood priming.

Only the SSO_2 Catheter that is supplied with the TherOx DownStream System may be used to deliver the SSO_2 therapy.

The DownStream® System, DownStream® Cartridge and SSO_2 Catheter set-up are shown in **Figures 1 through 4:**

Figure 1. TherOx® DownStream® System

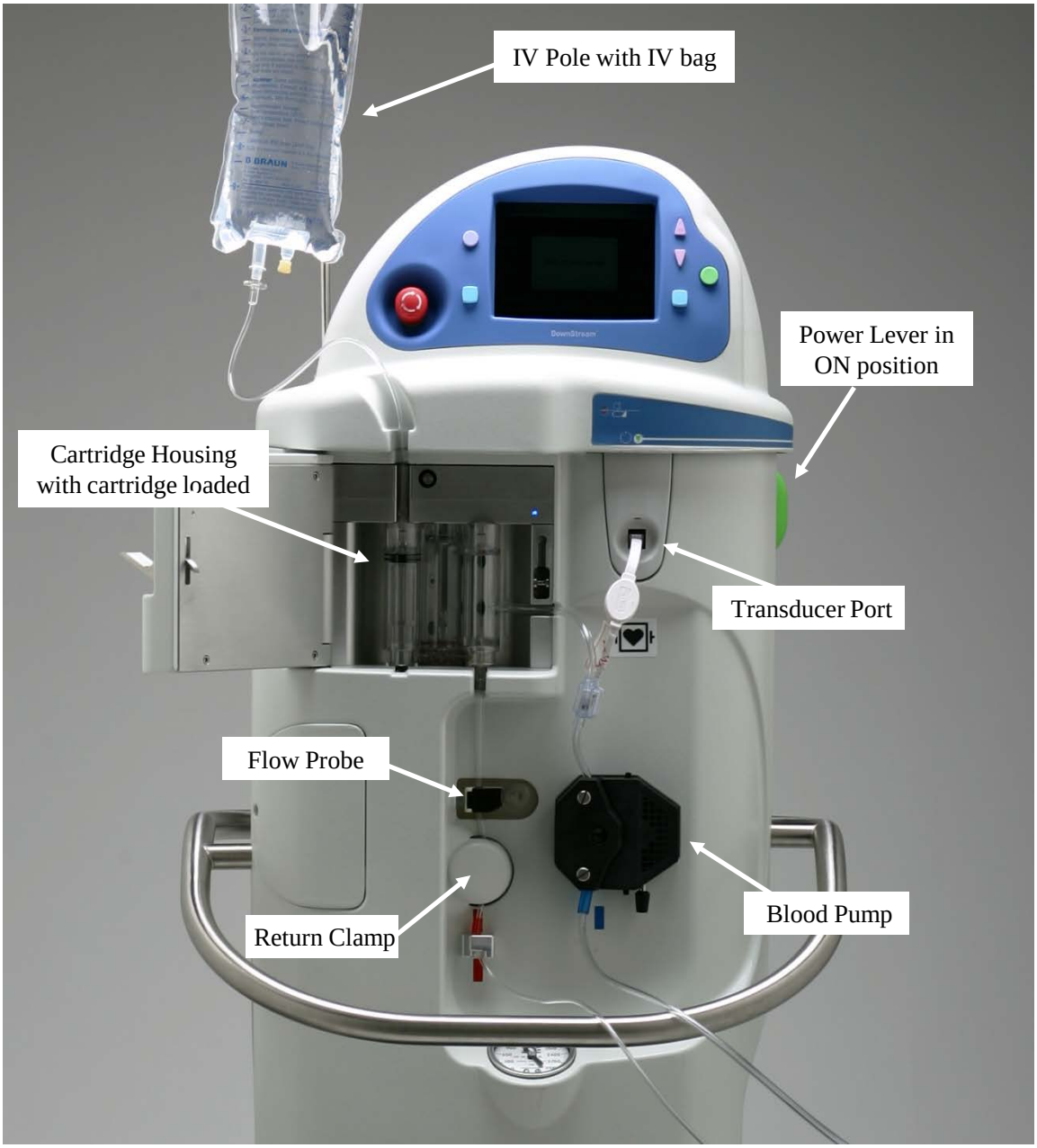

Figure 2. Close-up of DownStream® System Components

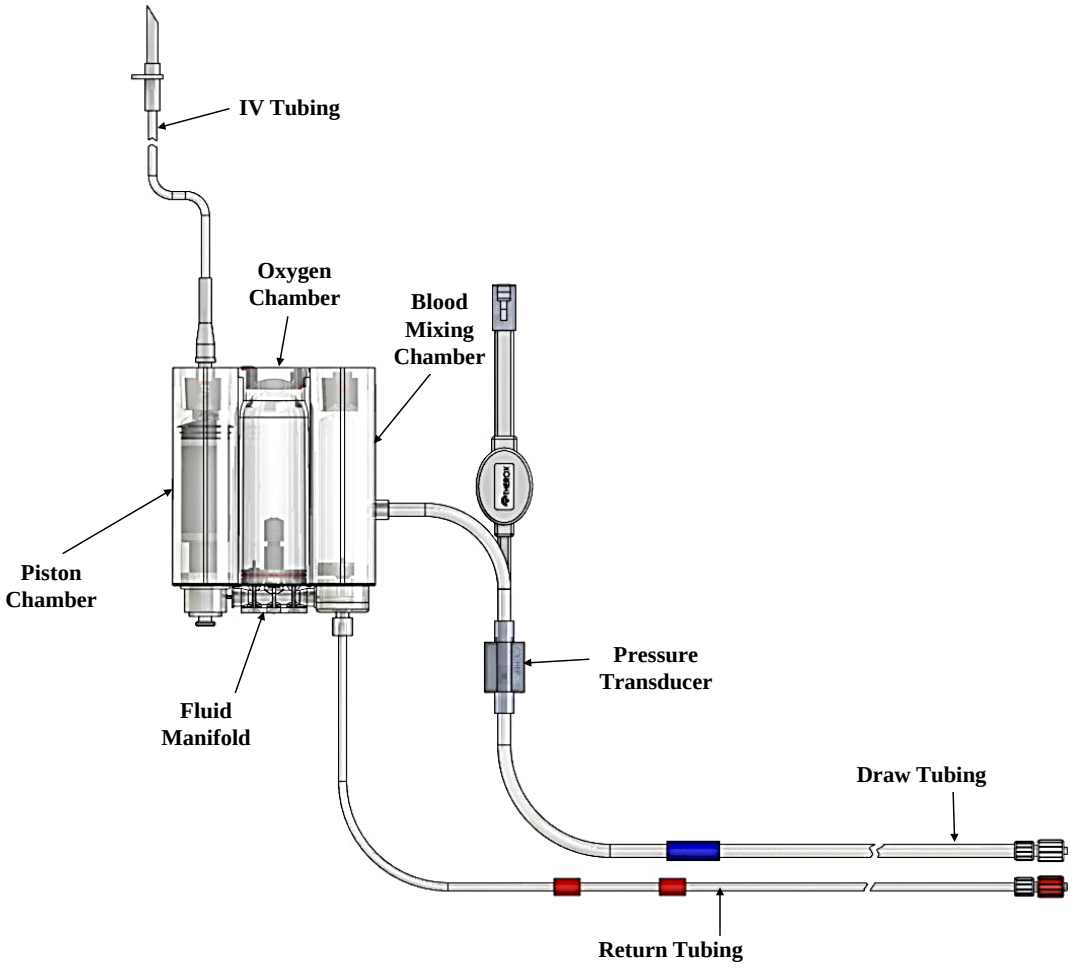

Figure 3. TherOx® DownStream® Cartridge

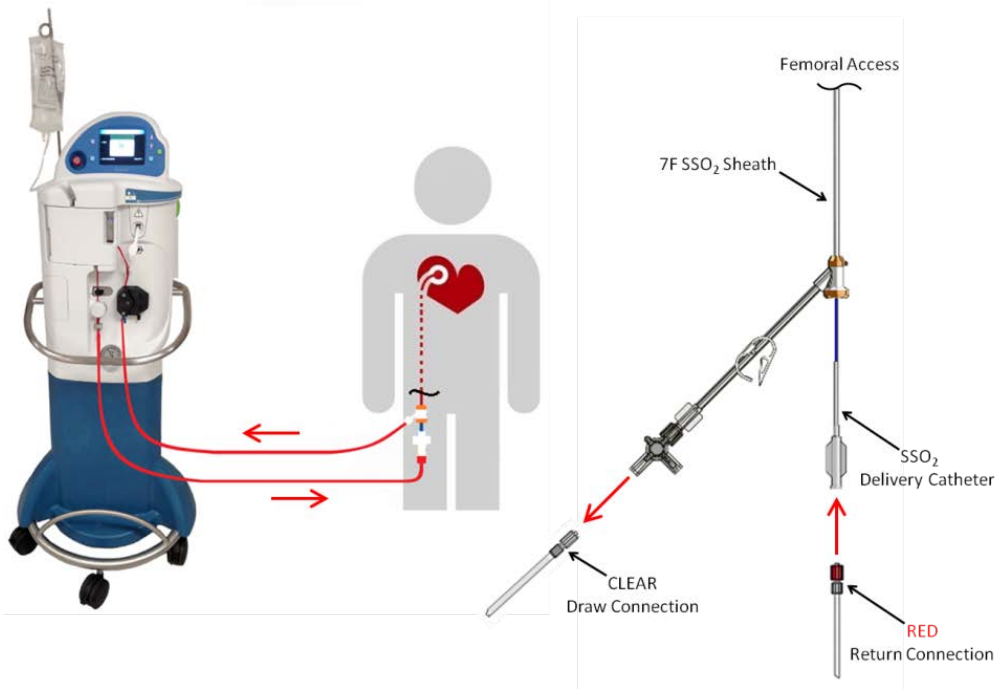

Figure 4a. SSO_2 Catheter Set-Up (coaxial femoral access site approach)

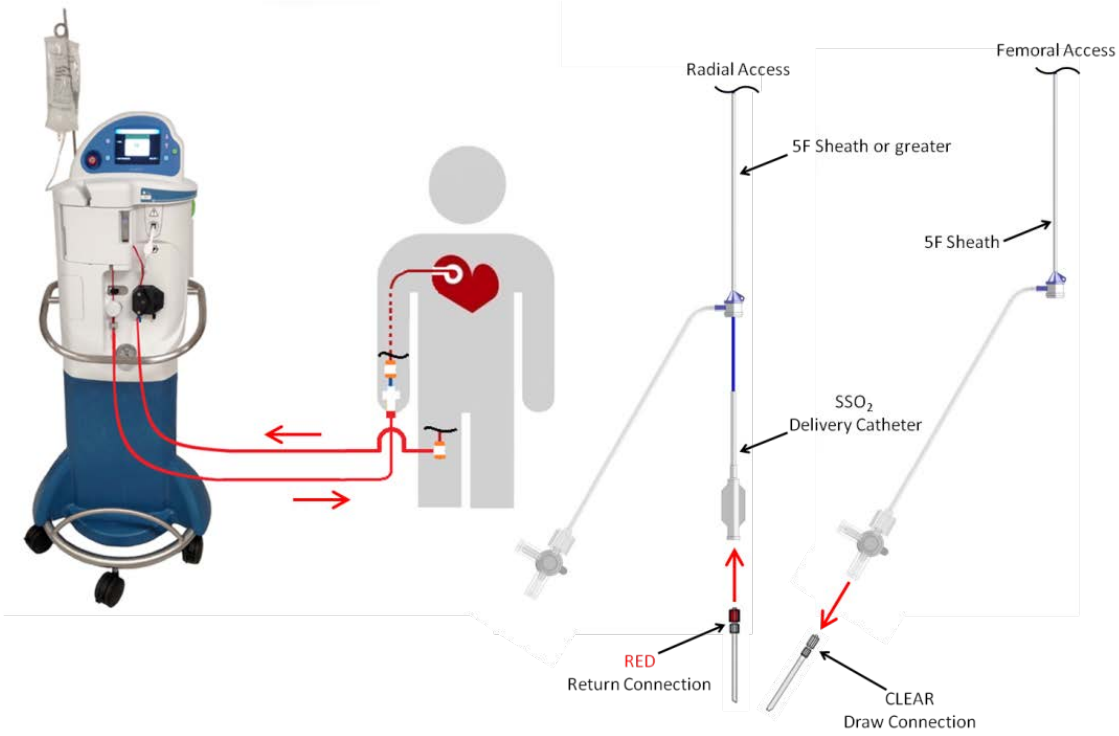

Figure 4b. SSO_2 Catheter Set-Up (radial access site delivery –femoral access site draw approach)

Patient Selection Criteria

- Patient must be ≥ 18 years and ≤ 80 years of age.
- Within 6 hours from symptom onset to successful reperfusion by means of PCI with stenting of left anterior descending coronary artery ST-elevation AMI.
- Successful revascularization by means of PCI with stenting as documented by < 50% diameter residual stenosis and TIMI flow grade II or III in the target vessel.
- Systemic arterial pO_2 greater than or equal to 10.7 kPa or 80 mmHg with supplemental oxygen.

Equipment Requirements

Quantity	Equipment
1	DownStream System – Model DS-1
1	DownStream Cartridge – Model DSC-2
1	SSO_2 Catheter
1 liter	Physician-prescribed, sterile physiologic 0.9% normal saline
1	"E" cylinder, or equivalent size of in-hospital, medical-grade oxygen with at least 800 psig (54.4 bar) pressure.
1	Guidewire, maximum OD 0.038 inch (0.97mm)
1	Coaxial approach: 7F** Merit Medical Custom Sheath Introducer Kit (K15-00147) or 8F introducer sheath with sidearm- or - Contralateral approach: 5F (minimum) introducer sheath
7-8	3 ml syringes
1-2	5 ml syringes

** 7F Merit Medical Custom Sheath Introducer Kit has a larger diameter sidearm to allow for required high flow blood draw. No other 7F sheath can be used.

Summary of Clinical Studies

AMIHOT II Clinical Trial

The applicant performed a clinical study to establish a reasonable assurance of safety and effectiveness of SSO_2 Therapy with the TherOx DownStream System for reducing infarct size in anterior AMI patients treated within six hours of symptom onset in the US under IDE G980257. Data from this clinical study were part of the basis for the PMA approval decision. A summary of the clinical study is presented below.

Study Design

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 at 20 investigational sites.

The study was a prospective, multicenter randomized clinical study of SSO_2 Therapy with the TherOx DownStream System compared to PCI/stenting alone to determine whether intracoronary perfusion of hyperoxemic blood SSO_2 Therapy group immediately after successful PCI/stenting for the treatment of acute myocardial infarction reduces the area of infarction (% left ventricle) at 14 days post-PCI, with no more than a 6% (absolute) increase in the incidence of Major Adverse Cardiac Events (MACE), death, re-infarction, target vessel revascularization, and stroke at the latter of either 30 days post-PCI or hospital discharge.

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. DSMB membership consisted of three (3) interventional cardiologists, one (1) non-interventional cardiologist and one (1) biostatistician.

1. Clinical Inclusion and Exclusion Criteria

Enrollment in the AMIHOT II study was limited to patients who met the following inclusion criteria:

Pre-PCI:

1. Patient must be ≥ 18 years of age
2. AMI must be anterior
3. Patient is experiencing clinical symptoms consistent with anterior AMI of < 6 hour duration from time of symptom onset until admission to the emergency room
4. Complete medical history, history of AMI, previous coronary interventions, list of medications given within last 24 hours are available
5. 12-lead qualifying ECG criteria: Anterior infarction (ST-segment elevation ≥ 1 mm in two or more contiguous leads between V1 and V4 or new left bundle branch block (LBBB) with documentation of LAD system culprit lesion)
6. Patient provides written Informed Consent
7. Patient and his/her physician agree to all required follow-up procedures and visits
8. Women of childbearing potential who have a negative pregnancy test (applies to female patients only)

Angiographic Inclusion Criteria: Evaluated after the subject provided signed Informed Consent but prior to randomization:

9. Based on coronary anatomy, PCI is indicated for culprit lesion with anticipated use of an Intra-Coronary Stent

10. TIMI 0, I, or II flow is present on the initial angiographic injection of the infarct-related artery
11. Successful angioplasty as documented by < 50% diameter residual angiographic stenosis within and associated with the culprit lesion and ≥ TIMI II flow and no major complications such as perforation or shock
12. Documented time of reperfusion is ≤ 6 hours from the documented time of symptom onset

Patients were not permitted to enroll in the AMIHOT II study if they met any of the following exclusion criteria:

Pre PCI:

1. Patients with ventricular pseudoaneurysm, VSD, or papillary muscle rupture.
2. Absolute contraindications to anticoagulant therapy, including hemorrhagic diathesis or thrombocytopenia
3. Systemic Arterial pO_2 is < 80 mmHg with supplemental oxygen
4. Placement of an intra-aortic balloon pump (IABP)
5. Patient has had coronary bypass surgery during the 30 day period preceding PCI
6. Severe known cardiac valvular stenosis or insufficiency, pericardial disease, or non-ischemic cardiomyopathy
7. Patients requiring cardiopulmonary resuscitation for > 10 minutes
8. Cardiogenic shock (SBP < 80 mm Hg for more than 30 minutes unresponsive to fluids or requiring intravenous pressors or placement of an IABP)
9. Expected survival of less than 6 months due to non-cardiac condition
10. Current participation in other investigational device or drug trials that have not finished the primary efficacy endpoint follow-up parameters
11. Patient has had a hemorrhagic stroke during the 6 month period preceding PCI
12. Physician discretion regarding unacceptability for enrollment

Angiographic Exclusion Criteria: Evaluated after the subject provided signed Informed Consent but prior to randomization:

13. Any proximal coronary diameter stenosis > 40 % that would restrict native flow with the infusion catheter in place
14. Infarct-related vessels that are either saphenous vein grafts and/or small second order coronary vessels that do not supply significant areas of myocardium
15. Presence of a non-stented coronary dissection upon completion of the PCI procedure
16. Unprotected left main diameter stenosis > 60%
17. Severe target vessel calcification or tortuosity
18. Multi – vessel disease that in the judgment of the investigator is best treated with emergent or urgent CABG or additional PCI within 30 days

19. In the investigator's opinion, the target vessel is unsuitable for either placing the infusion catheter or treatment with PCI.

2. Follow-up Schedule

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. Cardiac enzyme levels and diagnostic information were collected from blood samples obtained at 8, 16 and 24 hours post-PCI. **Table 1** summarizes the required schedule for AMIHOT II study assessments.

Table 1. AMIHOT II Study Assessments

	H&P/Consent	24-Hour ECG	Angiogram	Blood Labs	Blood Pressure	Arterial Blood Gas (ABG)	Heart rate/rhythm	ACT	Sestamibi Imaging	Follow-up Visit	Telephone Survey
Enrollment Screening/ Baseline	♥	♥ CONTINUOUS				♥					
Pre-PCI/Stent			♥	♥				♥			
Post PCI/Stent			♥	♥	♥	♥	♥	♥			
30 min. SSO_2 Infusion					♥	♥	♥	♥			
60 min. SSO_2 Infusion					♥	♥	♥	♥			
90 min. SSO_2 Infusion					♥	♥	♥	♥			
8 hours ± 2 hours				♥							
16 hours± 2 hours				♥							
24 hours± 2 hours				♥							
14 days± 7 days									♥		
30 days +15 days										♥	
6 months±30 days											♥
12 months± 30 days											♥

Shaded fields do not apply to Control subjects

3. Clinical Endpoints

The Primary Effectiveness Endpoint was infarct size as measured by percent of left ventricular mass, assessed by Tc-99m Sestamibi SPECT imaging at 14 days post PCI/stenting. The primary effectiveness endpoint was evaluated using a pre-specified superiority hypothesis.

The Primary Safety Endpoint was 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 primary safety endpoint was evaluated using a pre-specified non-inferiority hypothesis. All Serious Adverse Events (regardless of device-relatedness) were reported.

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). 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 informed borrowing of data from the previously completed AMIHOT I trial. The AMIHOT I trial examined both inferior and anterior AMI patients treated within 24 hours 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 primary effectiveness and safety endpoints. An unbalanced randomization ration of 2.8:1 (SSO_2 Therapy: Control) was utilized to satisfy the power requirements of the statistical model.

Accountability of PMA Cohort

A total of 301 patients enrolled in the AMIHOT II study, 222 patients randomized to the SSO_2 Therapy group and 79 patients to the Control group.

Study Population Demographic and Baseline Characteristics

Tables 2 and **3**, shown below, display median data for baseline patient characteristics and catheterization laboratory procedural results. Angiographic data were evaluated by an independent core laboratory, the Cardiology Research Foundation (CRF).

Table 2. 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%

	Control Group (N=79)	SSO_2 Therapy Group (N=222)
Current Smoking	43.0%	38.3%
Prior Myocardial Infarction	8.9%	9.0%
Prior PCI of target vessel	10.1%	5.9%

The patient population treated in the AMIHOT clinical trials is comparable to a typical acute myocardial infarction clinical trial population, in terms of age and gender breakdowns.

Table 3. 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%	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%
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 3 shows that the study groups are well matched in terms of catheterization laboratory procedural characteristics as well. Time interval data for door-to-balloon, symptom onset to emergency room arrival, and symptom onset to reperfusion times are longer for the SSO_2 Therapy group. Other procedural characteristics, including infarct lesion location, baseline left ventricular ejection fraction (LVEF), stent implantation, and incidence of rescue PCI cases showed similarity between the study groups. TIMI Grade 3 flow was more prevalent in the Control group pre-PCI, while Grade 0/1 flow was more prevalent in the SSO_2 arm. TIMI Grade 3 flow was more prevalent in the Control arm after PCI.

Safety and Effectiveness Results

Effectiveness

The AMIHOT II study results demonstrated superiority of SSO_2 Therapy compared to Control in median infarct size (26.5% of the left ventricular mass in the Control group; 20.0% in the SSO_2 Therapy group). The Bayesian posterior probability of superiority is 95.1% for study success based on an analysis of available data; when the study results for missing data were imputed using pre-specified methods, the posterior probability of superiority is 96.9%. These results are shown below in **Table 4**.

Table 4. Infarct Size at 14 Days (% of Left Ventricle), Bayesian Evaluation of Primary Endpoint, Sensitivity of Imputation Methods[†]: Pre-specified Model
(infarct size values presented on log-transformed scale with mean and standard error (SE))

	Control Group (mean ± SE) ($n^{§}$)	**AO Therapy Group** (mean ± SE) ($n^{§}$)	**Difference**[#] (± SE)	**Posterior Probability of Superiority***
ITT Analysis				
No imputation (available data)	3.42 ± 0.06 (n=52/68; 72)	3.30 ± 0.04 (n=49/71; 209)	-0.12 ± 0.07	95.1%
1st Order Imputation	3.42 ± 0.06 (n=53/79; 79)	3.30 ± 0.04 (n=52/81; 222)	-0.12 ± 0.07	95.5%
2nd Order Imputation	3.43 ± 0.06 (n=53/79; 79)	3.30 ± 0.04 (n=52/81; 222)	-0.13 ± 0.07	96.9%
PP Analysis[‡]	3.40 ± 0.06 (n=52/68; 69)	3.28 ± 0.04 (n=44/65; 175)	-0.12 ± 0.07	95.2%

[†]Analysis performed three ways: No imputation, 1st order imputation, 2nd order imputation methods

[‡]No imputation (available data)

[§]Sample size for Bayesian Evaluation given as (x/y; z) where x = number of Anterior $\leq$ 6 hours in AMIHOT I, y = number of other subjects in AMIHOT I and z = number of subjects in AMIHOT II (all Anterior $\leq$ 6 hours).

[#]Posterior mean difference between AO and Control groups incorporating data from AMIHOT I study into the hierarchical model.

*Posterior probability that the average AO Therapy Group infarct size is smaller than the Control Group infarct size.

Table 5 shows the AMIHOT II infarct size results by group, and for key subgroups.

Table 5. Infarct Size at 14 Days (% of Left Ventricle), Evaluation of Infarct Size for AMIHOT II ITT Analysis†
(infarct size values presented as median data with interquartile range (IQR))

	Control Group (n=79) (median ± IQR) (n)	**SSO_2 Therapy Group** (n=222) (median ± IQR) (n)
All Patients	26.5 ± 35.5 (n=72)	20 ± 31 (n=209)
Time strata (randomized)		
0 – 3 hrs to reperfusion	31 ± 35 (n=37)	15.5 ± 30.5 (n=96)
> 3 hrs to reperfusion	24 ± 35 (n=35)	24 ± 30 (n=113)
Time strata (actual)		
0 – 3 hrs to reperfusion	32 ± 35 (n=41)	14 ± 27 (n=88)
> 3 hrs to reperfusion	21 ± 30 (n=31)	26 ± 32 (n=121)
Infarct location (randomized)		
Proximal LAD	28 ± 37 (n=35)	25 ± 32 (n=117)
Non-proximal LAD	23 ± 35 (37)	14 ± 28 (n=92)
Infarct location (actual)		
Proximal LAD	29.5 ± 36 (n=34)	30 ± 33.5 (n=100)
Non-proximal LAD	21.5 ± 30 (n=38**)**	14 ± 26 (n=109)
Age		
Age < 60 (median)	20 ± 35 (n=42)	21 ± 30 (n=101)
Age ≥ 60 (median)	29.5 ± 36 (n=30)	19 ± 32 (n=108)
Gender		
Male	24 ± 36 (n=65)	20 ± 31 (n=167)
Female	38 ± 27 (n=7)	20.5 ± 23 (n=42)
Prior Myocardial Infarction		
Prior MI	37 ± 39 (n=6)	32 ± 32 (n=19)
No Prior MI	24 ± 36 (n=65)	19 ± 29 (n=189)
Diabetes		
Diabetic (Type I or II)	20 ± 39 (n=10)	21 ± 26.5 (n=32)
Non-diabetic	28 ± 35 (n=61)	19.5 ± 31 (n=172)

†Available data for ITT patients analyzed as per Statistical Analysis Plan

Safety

The primary safety endpoint evaluated for non-inferiority using a Bayesian hierarchical model that considered 30-day MACE data from the AMIHOT I and II studies. The primary safety analysis demonstrated statistical non-inferiority, with the Bayesian posterior probability of non-inferiority being 99.5%, successfully achieving the study endpoint. In the AMIHOT II trial, the 30-day MACE rates were 3.8% in the Control group and 5.4% in the SSO_2 group. The MACE component rate data are displayed in **Table 6**.

Table 6. AMIHOT II 30-day MACE Rates

	Events				
Group	**Death**	**Reinfarction**	**TVR**	**Stroke**	**Composite MACE # Patients (%)**
Control (n = 79)	0	2	3	0	**3 (3.8%)**
SSO_2 Therapy (n = 222)	**4**	**6**	**9**	**0**	**12 (5.4%)**

Overall 30-day adverse event data for the AMIHOT II trial are presented in **Table 7**.

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 experienced one or more adverse events. 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 may have contributed to the higher adverse events rate observed in the SSO_2 arm (**Table 7**).

Table 7. AMIHOT II 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%)	255	118 (53.2%)
SSO_2 device related AE			0	0 (0%)
SSO_2 procedure related AE			45	39 (17.6%)
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%)	1	1 (0.5%)
Other relationship*	18	15 (19.0%)	63	47 (21.2%)
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%)

	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**
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*	6	5 (6.3%)	10	10 (4.5%)
Unknown relationship	0	0 (0%)	3	3 (1.4%)
Adverse Event related to AMIHOT II Vessel	8	5 (6.3%)	26	20 (9.0%)
*Including pre-existing condition, concurrent condition, concurrent intervention and other relationships				

Table 8 summarizes bleeding events within 30 days by comparing the two study groups. These events were adjudicated by the Clinical Events Committee and categorized 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

An increase in all bleeding events was observed in the SSO_2 Therapy group as compared to the Control group (24.3% vs. 12.7%).

Table 8. AMIHOT II 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%)	57	54 (24.3%)
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%)	16	15 (6.8%)
	Mild	Anemia	0	0 (0%)	5	5 (2.3%)
		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 addition to bleeding, the adverse events of death, myocardial rupture, and stent thrombosis Were also higher in the SSO_2 arm of AMIHOT II (**Table 9)**.

Table 9. Safety Events of Interest (AMIHOT II)

Event	**Control Group** (n=79) n (%)	**SSO_2 Therapy Group** (n=222) n (%)
Death	0 (0.0%)	4 (1.8%)
Myocardial Rupture	0 (0.0%)	2 (0.9%)
Stent thrombosis	2 (2.5%)	9 (4.1%)
Bleeding (any)	10 (12.7%)	54 (24.3%)

After completing improvements to the hardware console and simplifying the catheter delivery system, additional data for SSO_2 Therapy was obtained from follow-up clinical studies.

IC-HOT Clinical Trial

The IC-HOT clinical trial was designed to confirm the safety and efficacy results of SSO_2 Therapy in 100-patient IDE study in the target patient population.

Study Design

Patients were treated between February 16, 2016 and May 2, 2017. The data were collected through May 17, 2018 and included 100 patients. There were 15 investigational sites.

IC-HOT was a non-randomized, single-arm study. Subjects with anterior STEMI requiring stent placement in the proximal and/or mid LAD who met all inclusion and exclusion criteria were treated with primary PCI with stenting; if successful and uncomplicated, PCI with stenting was immediately followed with post-procedure delivery of SSO_2 Therapy for a duration of 60 minutes.

An independent Clinical Events Committee (CEC) reviewed and adjudicated all key, pre-specified adverse events.

An independent Data Safety Monitoring Board (DSMB) reviewed and assessed overall study safety both during and at the conclusion of the study.

The Cardiovascular Research Foundation's Angiographic and MRI Core Laboratories evaluated patient angiographic and MRI scan data for the IC-HOT study.

Clinical Inclusion and Exclusion Criteria

Candidates in the IC-HOT study must have met ALL the following general inclusion criteria:

Pre-PCI:

1. The subject must be ≥18 and ≤80 years of age.

2. AMI must be anterior (ST-segment elevation ≥1 mm in two or more contiguous leads between V1 and V4 or new left bundle branch block).
3. Subject is experiencing clinical symptoms consistent with acute MI of ≤6 hour duration from time of symptom onset until admission to the emergency room.
4. The subject or legally authorized representative has been informed of the nature of the study, agrees to its provisions and has been provided and signed written informed consent, approved by the appropriate Institutional Review Board (IRB).
5. Subject and his/her physician agree to all required follow-up procedures and visits.

Angiographic Inclusion Criteria: Evaluated after the subject provided signed Informed Consent but prior to enrollment:

6. Based on coronary anatomy, PCI is indicated for revascularization of the culprit lesion(s) with use of a commercially available coronary stent (bare metal or drug-eluting, at operator discretion) in the LAD.
7. The primary stented infarct-related lesion(s) must be in the proximal and/or mid-LAD coronary artery (other lesions in the LAD target vessel, including diagonal branches, may be treated if clinically indicated).
8. Baseline (pre-PCI) TIMI flow grade 0, 1, 2, or 3 flow in the LAD.
9. Successful angioplasty is completed ≤6 hrs from symptom onset, as documented by <50% diameter residual angiographic stenosis within all treated culprit lesions with TIMI 2 or 3 flow and no major complications such as perforation or shock.
10. Expected ability to place the SSO_2 delivery catheter in the coronary ostium of the left main coronary system to deliver SSO_2 Therapy with stable, coaxial alignment.

Patients were not permitted to enroll in the IC-HOT study if they met any of the following exclusion criteria:

Pre-PCI:

1. Prior CABG surgery.
2. Prior myocardial infarction, or known prior systolic dysfunction (known ejection fraction <40% by any prior measure or regional wall motion abnormalities; this criterion does not include left ventricular dysfunction induced by the acute MI).
3. Thrombolytic therapy administered for this STEMI.
4. An elective surgical procedure is planned that would necessitate interruption of anti-platelet agents during the first 30 days post-enrollment.
5. Subjects who previously underwent coronary stent implantation and in whom coronary angiography demonstrates stent thrombosis to be the cause of the anterior AMI.
6. Subjects who have previously undergone an angioplasty or stenting procedure in the left anterior descending coronary artery.
7. Subjects with ventricular pseudoaneurysm, VSD, or severe mitral valve regurgitation (with or without papillary muscle rupture).
8. Any contraindication to MRI imaging. This will include any of the following exclusions:

a. Cardiac pacemaker or implantable defibrillator;
b. Non-MRI compatible aneurysm clip;
c. Neural Stimulator (i.e., TENS unit);
d. Any implanted or magnetically activated device (insulin pump);
e. Any type of non-MRI compatible ear implant;
f. Metal shavings in the orbits;
g. Any metallic foreign body, shrapnel, or bullet in a location which the physician feels would present a risk to the subject;
h. Any history indicating contraindication to MRI, including claustrophobia or allergy to gadolinium;
i. Inability to follow breath hold instructions or to maintain a breath hold for >15 seconds; and
j. Known hypersensitivity or contraindication to gadolinium contrast.

9. Known impaired renal function (creatinine clearance <30 ml/min/1.73 m^2 by the MDRD formula) or on dialysis.
10. Known platelet count <100,000 cells/mm^3 or >700,000 cells/mm^3 or a known Hgb <10 g/dL.
11. Subject has active bleeding or a history of bleeding diathesis or coagulopathy (including heparin induced thrombocytopenia), or refusal to receive blood transfusions if necessary.
12. History of intracerebral mass, aneurysm, arteriovenous malformation, or hemorrhagic stroke.
13. Stroke or transient ischemic attack within the past six (6) months, or any permanent neurological defect.
14. Gastrointestinal or genitourinary bleeding within the last two (2) months, or any major surgery (including CABG) within six weeks of enrollment.
15. Subject has received any organ transplant or is on a waiting list for any organ transplant.
16. Subject has other medical illness (e.g., cancer, dementia) or known history of substance abuse (alcohol, cocaine, heroin, etc.) that may cause non-compliance with the protocol, confound the data interpretation, or is associated with limited life expectancy of less than one year.
17. Subject has a known hypersensitivity or contraindication to unfractionated heparin, abciximab, aspirin, bivalirudin, cangrelor, clopidogrel, ticlopidine, prasugrel, eptifibatide, tirofiban or ticagrelor that cannot be adequately premeditated.
18. Current use of warfarin, dabigatran, or factor Xa inhibitors, or known intent to administer these agents after the primary PCI.
19. Subjects presenting with or developing in the cath lab prior to completion of the primary PCI procedure any of the following conditions: cardiogenic shock (SBP <80 mmHg for >30 minutes), or requiring IV pressors or emergent placement of an intra-aortic balloon pump (IABP), Impella, or other hemodynamic support for hypotension treatment, or cardiopulmonary resuscitation for >10 minutes, or ventricular fibrillation or tachycardia requiring cardioversion or defibrillation.

20. Severe known cardiac valvular stenosis or insufficiency, pericardial disease, or non-ischemic cardiomyopathy.
21. Any significant medical or social condition which in the investigator's opinion may interfere with the subject's participation in the study or ability to comply with follow-up procedures, including MRI (e.g. alcoholism, dementia, lives far from the research center, etc.).
22. Current participation in other investigational device or drug trials.
23. Previous enrollment in this study.

Angiographic Exclusion Criteria: Evaluated after the subject provided signed Informed Consent but prior to enrollment:

24. Anticipated inability to achieve a stable coaxial position in the left main coronary artery with the SSO_2 delivery catheter.
25. Treatment during the index procedure of any lesion in either the left main, LCX (including the ramus), and/or RCA.
26. Post-index procedure planned intervention within 30 days (i.e., PCI of non-target lesions in any vessel, or CABG). Note: Planned revascularization (PCI or bypass) of a non-target lesion >30 days following the index procedure is allowed.
27. Anterior MI is due to thrombosis within or adjacent to a previously implanted stent.
28. Left ventriculography demonstrates severe mitral regurgitation, a ventricular septal defect, or a pseudoaneurysm.
29. Any left main coronary artery stenosis >20%.
30. Any untreated LAD or diagonal branch lesion is present with diameter stenosis $\geq$ 50% in a vessel with reference vessel diameter > 2.0 mm (visually estimated), or for which PCI will be required before the MRI study.
31. Presence of a non-stented coronary dissection with NHLBI grade $\geq$B upon completion of the PCI procedure.

1. Follow-up Schedule

Baseline, procedural, post-procedure, in-hospital, and 30-day clinical follow-up were performed. Cardiac MRI was performed at 4 (±1) days and at 30 days (±7 days) to collect device effectiveness data. Primary data collection including adverse event reporting was through 30 days; patient safety was tracked and reported through one year.

The IC-HOT schedule of study assessments is presented in **Table 10**.

Table 10. Schedule of IC-HOT Assessments

PROCEDURE / TEST	Pre-PCI - Stent	PCI / Stent Procedure	Post- PCI / Stent	Baseline SSO_2	30 min SSO_2	60 min SSO_2	60 (±30) min post-SSO_2	12 (±2) hrs	24 (±2) hrs	Cardiac MRI (4 ± 1 days)	30 (±7) days	6 and 12 mos (±30 days)
Subject Medical / Clinical History / Physical Exam	√											
Subject Informed Consent	√											
General Inclusion / Exclusion Criteria	√											
Angiographic Inclusion / Exclusion Criteria			√									
Cardiac Enzymes: CK, CK-MB, and Troponin	√							√	√	√[1]		
Arterial blood gas				√								
WBC, hemoglobin, creatinine, platelet count	√[8]								√[2]			
Cardiac MRI										√[3]	√[4]	
HR, BP	√	√	√	√	√	√						
ECG	√						√[5]			√	√	
Anticoagulation (per protocol)	√											
Antiplatelet loading dose	√											
Cardiac cath lab procedures and information		√										
Cine angiogram w/o contrast of angiographic delivery catheter				√	√	√						
Coronary angiogram with TIMI flow grade assessment	√	√[6]	√			√						
ACT (per protocol)		√		√	√[9]	√						
SSO_2 Therapy Procedure			√	√	√	√						
Per Protocol Medications	√	√	√	√	√	√		√			√	√
Dual Antiplatelet Medication	√	√	√					√[7]			√[7]	√
Concomitant Cardiac Medications	√	√	√	√	√	√		√			√	√
Adverse Events				√	√	√	√	√	√	√	√	√

2. Clinical Endpoints

The primary endpoint for the IC-HOT study evaluated safety, using the 30-day rate of the composite Net Adverse Clinical Events (NACE). NACE events were the following:

- Death (all-cause)
- Reinfarction
- Target Vessel Revascularization (clinically driven)
- TIMI major or minor bleeding
- New onset severe heart failure or rehospitalization for heart failure
- Stent thrombosis (ARC definite or probable)

This composite endpoint includes safety categories that are of significance in contemporary AMI studies. The IC-HOT study used well-established clinical event definitions for the component NACE event categories.

The threshold for assessing success of the Primary Endpoint was that the observed 30-day NACE rate in IC-HOT be no greater than the 30-day NACE rate observed in the control arm of a contemporaneous study, INFUSE-AMI[1]. The INFUSE-AMI study included a similar population of anterior wall STEMI patients with anticipated time to reperfusion less than five hours. INFUSE-AMI included a 2x2 treatment matrix with subjects receiving PCI w/stenting standard of care, with or without intracoronary abciximab and with or without intracoronary aspiration. The threshold rate of 10.7% was derived from a *post hoc* analysis of 112 INFUSE-AMI control subjects who had received neither aspiration nor intracoronary abciximab.

In addition, the specific 30-day NACE event categories of death, stent thrombosis, myocardial rupture, and bleeding were examined as individual events. **Table 11** below shows FDA-recommended 30-day event rate benchmarks for these individual adverse events.

Table 11. FDA Guidelines for Acceptable Adverse Event Rates

30-Day NACE Event	**IC-HOT Trial FDA Guideline**
Death	≤3.0%
Stent Thrombosis	≤3.0%
Myocardial Rupture	≤1.0%
TIMI Major and Minor Bleeding	≤3.0%

Accountability of the PMA Cohort

At the time of database lock, of the 100 patients enrolled in the IC-HOT study, 100% (n=100) of patients were available for analysis at the completion of the study, the 30-day post-procedural visit.

Study Population Demographics and Baseline Characteristics

The patient baseline characteristics shown in **Table 12** are consistent with an anterior STEMI population and the previously conducted AMIHOT II study.

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[1] Stone GW, Maehara A, Witzenbichler B, et al. Intracoronary abciximab and aspiration thrombectomy in patients with large anterior myocardial infarction: the INFUSE-AMI randomized trial. *JAMA* 2012 May 2;307(17):1817-26.

Table 12. IC-HOT Baseline Patient Characteristics

	SSO_2 Therapy Group (N=100)
Age (years)	59.5
Male	83%
Diabetes	26%
Hypertension	55%
Hyperlipidemia	51%
Current Smoking	41%

Safety and Effectiveness Results

As shown in **Table 13**, IC-HOT had a median door-to-balloon time of 62 min and a median time from symptom onset to reperfusion of 138.5 min. Patients were evenly distributed between proximal or mid-LAD target lesion location. Angiographic core laboratory analysis of TIMI flow grade data showed that 16.2% of subjects remained with TIMI Grade 2 flow after PCI and stenting.

Table 13. IC-HOT Cardiac Catheterization Laboratory Procedural Results (pre-enrollment)

	SSO_2 Therapy Group (N=100)
Time intervals (min):	
Symptom Onset to ER arrival	67.5
Door to Balloon	62.0
Symptom Onset to reperfusion	138.5
Infarct lesion location:	
Proximal LAD**	44.6%
Mid LAD	55.4%
Stent implanted	100%
Glycoprotein IIb/IIIa inhibitor use	46.0%
TIMI flow pre-PCI:* **	
0/1	60.0%
2	30.0%
3	10.0%
TIMI flow post-PCI:* **	
0/1	0.0%
2	16.2%
3	83.8%

**LAD = left anterior descending coronary artery

***as determined by independent angiographic core laboratory

1. Safety Results

The results for the primary composite safety endpoint (**Table 14**) show that 7.1% (7/98) of subjects experienced a qualifying NACE event within 30 days of the index procedure (two subjects were lost to follow up). The point estimate of NACE rate was below the threshold limit of 10.7%.

Table 14. IC-HOT 30-Day Net Adverse Clinical Events (NACE) - CEC Adjudicated

Parameter	**SSO_2 Therapy n/N (%) (N=100*)**
NACE (death, reinfarction, clinically-driven target vessel revascularization, stent thrombosis (ARC definite or probable), new onset heart failure or readmission for heart failure, or TIMI major or minor bleeding)	7/98 (7.1%)
Death	0/98 (0.0%)
Cardiac	0/98 (0.0%)
Vascular	0/98 (0.0%)
Non-Cardiovascular	0/98 (0.0%)
Reinfarction/Spontaneous	1/98 (1.0%)
STEMI/NSTEMI	1/98 (1.0%)
STEMI	0/98 (0.0%)
NSTEMI	1/98 (1.0%)
Undetermined	0/98 (0.0%)
Q-wave/Non-Q-wave	1/98 (1.0%)
Q-wave	0/98 (0.0%)
Non-Q-wave	1/98 (1.0%)
Undetermined	0/98 (0.0%)
MI In the optimized SSO_2 therapy region (Target Vessel)	
In the optimized SSO_2 therapy region	0/98 (0.0%)
Not in the optimized SSO_2 therapy region	1/98 (1.0%)
Undetermined	0/98 (0.0%)
Clinically Driven Target Vessel Revascularization (TVR)	1/98 (1.0%)

Parameter	SSO_2 Therapy n/N (%) (N=100*)
PCI	1/98 (1.0%)
CABG	0/98 (0.0%)
Clinically Driven Target Lesion Revascularization (TLR)	1/98 (1.0%)
PCI	1/98 (1.0%)
CABG	0/98 (0.0%)
Clinically Driven Target Vessel/Non-Target Lesion Revascularization (TVR/NTLR)	1/98 (1.0%)
PCI	1/98 (1.0%)
CABG	0/98 (0.0%)
TIMI major or minor Bleeding	4/98 (4.1%)
Minor	4/98 (4.1%)
Major	0/98 (0.0%)
New onset severe heart failure or re-hospitalization for heart failure	1/98 (1.0%)
New onset heart failure	1/98 (1.0%)
Required hospitalization	1/98 (1.0%)
Re-hospitalization for previous heart failure	0/98 (0.0%)
ARC Definite/Probable Stent Thrombosis	1/98 (1.0%)
Acute	1/98 (1.0%)
Definite	1/98 (1.0%)
Probable	0/98 (0.0%)
Subacute	0/98 (0.0%)
Definite	0/98 (0.0%)
Probable	0/98 (0.0%)

*2 subjects missed 30-day follow up visits and were unavailable for the 30-day NACE assessment.

A summary of 30-day adverse events (**Table 15)** shows that 48.0% (48/100) of IC-HOT subjects experienced an adverse event within 30 days. 12.0% (12/100) of subjects experienced a serious adverse event within 30 days. These adverse event and serious adverse event rates were lower

than the rates observed in the AMIHOT II: 53.8% and 25.7% for the SSO_2 Therapy arm and 46.8% and 19.0% for the Control arm.

Table 15. IC-HOT 30-Day Summary of Adverse Events

Parameter	**SSO_2 Therapy n/N(%) (N=100)**
Any Adverse Event	48/100 (48.0%)
Non-Serious Adverse Event	43/100 (43.0%)
Serious Adverse Event	12/100 (12.0%)
Adverse Event Relationship	
Related to Device (system/cartridge)	0/100 (0.0%)
Related to SSO_2 procedure	2/100 (2.0%)
Related to Index PCI procedure	7/100 (7.0%)
Related to Coronary Artery Disease	21/100 (21.0%)
Was the adverse event related to the PCI target vessel	5/100 (5.0%)
Serious Adverse Event Relationship	
Related to Device (system/cartridge)	0/100 (0.0%)
Related to SSO_2 procedure	0/100 (0.0%)
Related to Index PCI procedure	3/100 (3.0%)
Related to Coronary Artery Disease	6/100 (6.0%)
Was the adverse event related to the PCI target vessel	2/100 (2.0%)

Table 16 provides detail of all 30-day events. Approximately 11.2% of IC-HOT subjects experienced a bleeding event (as compared to 24.3% of AMIHOT II SSO_2 Therapy subjects and 12.7% of AMIHOT II Control subjects). No patients with bleeding events required a transfusion.

Table 16. IC-HOT 30-Day Follow-up Clinical Outcomes

Parameter	**SSO_2 Therapy n/N(%) (N=100)**
Death	0/98 (0.0%)
Cardiac	0/98 (0.0%)
Non-Cardiac	0/98 (0.0%)

Parameter	SSO_2 Therapy n/N(%) (N=100)
Unknown	0/98 (0.0%)
Myocardial Infarction	1/98 (1.0%)
Spontaneous MI	1/98 (1.0%)
Periprocedural MI - PCI	0/98 (0.0%)
Periprocedural MI - CABG	0/98 (0.0%)
Reinfarction	0/98 (0.0%)
STEMI	0/98 (0.0%)
NSTEMI	1/98 (1.0%)
Undetermined	0/98 (0.0%)
Q-wave MI	0/98 (0.0%)
Non-Q-wave MI	1/98 (1.0%)
Undetermined	0/98 (0.0%)
MI in the Optimized SSO_2 Therapy Region	0/98 (0.0%)
Recurrent ischemic pain >20 minutes unrelieved by NTG	1/98 (1.0%)
ST segment elevation or depression	1/98 (1.0%)
Cardiac enzyme elevations	1/98 (1.0%)
Repeat Revascularization/Angiography	5/98 (5.1%)
Repeat Angiography only	4/98 (4.1%)
Repeat Revascularization	1/98 (1.0%)
Clinically Driven Target Lesion Revascularization (TLR)	1/98 (1.0%)
PCI	1/98 (1.0%)
CABG	0/98 (0.0%)
Clinically Driven Target Vessel/Non-Target Lesion Revascularization (TVR/NTLR)	1/98 (1.0%)
PCI	1/98 (1.0%)
CABG	0/98 (0.0%)

Parameter	SSO_2 Therapy n/N(%) (N=100)
Clinically Driven Non-Target Vessel Revascularization (NTVR)	0/98 (0.0%)
PCI	0/98 (0.0%)
CABG	0/98 (0.0%)
Stent Thrombosis	2/98 (2.0%)
Acute	2/98 (2.0%)
Subacute	0/98 (0.0%)
Definite	1/98 (1.0%)
Probable	0/98 (0.0%)
Possible	0/98 (0.0%)
Non-ARC	1/98 (1.0%)
Hemorrhagic/Vascular event	11/98 (11.2%)
Hemorrhage	6/98 (6.1%)
Hematoma	4/98 (4.1%)
Tamponade	0/98 (0.0%)
Arteriovenous Fistula	0/98 (0.0%)
Aneurysm/Pseudoaneurysm	0/98 (0.0%)
Myocardial rupture	0/98 (0.0%)
Vascular Damage	0/98 (0.0%)
Peripheral Ischemia	0/98 (0.0%)
Embolism	0/98 (0.0%)
Thrombosis	0/98 (0.0%)
TIMI Classification	
Minimal	6/98 (6.1%)
Minor	4/98 (4.1%)
Major	0/98 (0.0%)
GUSTO Bleeding Classification	

Parameter	SSO_2 Therapy n/N(%) (N=100)
Severe or life threatening	0/98 (0.0%)
Moderate	0/98 (0.0%)
Mild	10/98 (10.2%)
Suspected Congestive Heart Failure	10/98 (10.2%)
Symptoms (New or Worsening)	
Dyspnea	4/98 (4.1%)
Decreased exercise tolerance	2/98 (2.0%)
Fatigue	3/98 (3.1%)
Other symptoms of worsened end-organ perfusion	6/98 (6.1%)
Signs (New or Worsening)	
Peripheral edema	0/98 (0.0%)
Increasing abdominal distention or ascites	0/98 (0.0%)
Pulmonary rales/crackles/crepitations	2/98 (2.0%)
Increased jugular venous pressure and/or hepatojugular reflux	2/98 (2.0%)
S3 cardiac gallop	0/98 (0.0%)
Clinical significant or rapid weight gain thought to be related to fluid retention	0/98 (0.0%)
NYHA classification at presentation	
I	3/98 (3.1%)
II	4/98 (4.1%)
III	1/98 (1.0%)
IV	1/98 (1.0%)
Neurologic event	0/98 (0.0%)
Type of injury	
Ischemic	0/98 (0.0%)
Hemorrhagic	0/98 (0.0%)
Unknown	0/98 (0.0%)

Table 17 displays observed event rates for the pre-specified individual events of interest. The rates of 30-day mortality, stent occlusion, and myocardial rupture were lower than the respective FDA benchmarks. The rate of observed TIMI Major/Minor bleeding was higher than the benchmark; all bleeding events were classified as TIMI Minor.

Table 17. IC-HOT Events of Interest: 30-day Rates

FDA Recommended Guidelines for Acceptable Adverse Event Rates **30-Day AE**	**FDA Threshold**	**IC-HOT 100 Pt. safety study**
Death	**3.0%**	**0% (0/98)**
Stent Occlusion	**3.0%**	**1% (1/98)**
Myocardial Rupture	**1.0%**	**0% (0/98)**
SAE bleeding	**3.0%**	**4.1% (4/98) (TIMI Major/Minor Bleeding)**

2. Effectiveness Results

Cardiac MRI scans were required by protocol on day 4 (±1) and day 30 (±7).

Infarct Size Results

Cardiac MRI data are presented in **Table 18** for the day 4 and day 30 scans including the 30-day infarct size results (% of Infarct Mass of Myocardial Mass). The median (Q1, Q3) infarct size (%) was 19.4 (8.8, 28.9). This result is consistent with the AMIHOT II result for median (Q1, Q3) infarct size (%) = 20.0 (6, 37) for the SSO_2 Therapy group.

Table 18. IC-HOT MRI Analysis at 4 and 30 Days (All Treated Subjects Population)

Parameter	**Statistics**	**Day 4 SSO_2 Therapy** (N=88)	**Day 30 SSO_2 Therapy** (N=87)
Time from Index Procedure (day)	N	88	87
	Mean ± (StdDev)	4.0 ± 1.3	33.6 ± 12.1
	Median (Q1,Q3)	4.0 (3.0, 5.0)	30.0 (29.0, 34.0)
	Min,Max	1.0, 7.0	23.0, 113.0
Myocardial Mass (g)	N	86	85
	Mean ± (StdDev)	129.6 ± 34.4	114.0 ± 29.0
	Median (Q1,Q3)	128.0 (104.0, 149.0)	112.0 (93.6, 129.0)
	Min,Max	57.0, 249.0	57.7, 206.0
Area at Risk (g)	N	80	*
	Mean ± (StdDev)	50.3 ± 19.6	
	Median (Q1,Q3)	51.1 (34.8, 62.0)	
	Min,Max	0.0, 94.2	

Parameter	Statistics	Day 4 SSO_2 Therapy (N=88)	Day 30 SSO_2 Therapy (N=87)
% of Area at Risk of Myocardial Mass	N	80	*
	Mean ± (StdDev)	39.5 ± 11.8	
	Median (Q1,Q3)	38.2 (33.3, 47.4)	
	Min,Max	0.0, 63.2	
Salvage Mass (g)	N	72	*
	Mean ± (StdDev)	19.9 ± 11.9	
	Median (Q1,Q3)	18.7 (11.3, 26.4)	
	Min,Max	0.0, 71.0	
Infarct Mass (g)	N	78	85
	Mean ± (StdDev)	31.2 ± 19.2	21.9 ± 15.0
	Median (Q1,Q3)	29.5 (18.0, 46.9)	20.6 (10.2, 31.2)
	Min,Max	0.0, 74.8	0.0, 57.8
Number with Infarct Mass=0g	n/N (%)	4/78 (5.1%)	7/85 (8.2%)
MVO (g)	N	78	*
	Mean ± (StdDev)	2.1 ± 2.9	
	Median (Q1,Q3)	0.5 (0.0, 3.5)	
	Min,Max	0.0, 13.2	
Number with MVO=0	n/N (%)	35/78 (44.9%)	
% of Infarct Mass of Myocardial Mass	N	78	85
	Mean ± (StdDev)	23.8 ± 13.8	19.2 ± 12.5
	Median (Q1,Q3)	24.1 (14.4, 31.6)	19.4 (8.8, 28.9)
	Min,Max	0.0, 54.1	0.0, 46.4
% of Infarct Mass of Area at Risk	N	71	*
	Mean ± (StdDev)	57.2 ± 24.6	
	Median (Q1,Q3)	65.6 (42.9, 73.3)	
	Min,Max	0.0, 99.1	
% of Salvage Mass of Area at Risk	N	71	*
	Mean ± (StdDev)	42.8 ± 24.6	
	Median (Q1,Q3)	34.4 (26.7, 57.1)	
	Min,Max	0.9, 100.0	

Parameter	Statistics	Day 4 SSO_2 Therapy (N=88)	Day 30 SSO_2 Therapy (N=87)
% of MVO of Myocardial Mass	N	78	*
	Mean ± (StdDev)	1.5 ± 2.3	
	Median (Q1,Q3)	0.3 (0.0, 2.4)	
	Min,Max	0.0, 11.1	
% of MVO of Infarct Mass	N	74	*
	Mean ± (StdDev)	4.6 ± 5.6	
	Median (Q1,Q3)	1.9 (0.0, 8.4)	
	Min,Max	0.0, 21.1	
% of MVO of Area at risk	N	71	*
	Mean ± (StdDev)	3.3 ± 4.4	
	Median (Q1,Q3)	0.9 (0.0, 5.4)	
	Min,Max	0.0, 19.4	
Left Ventricular Ejection Fraction (%)	N	86	85
	Mean ± (StdDev)	41.7 ± 8.3	44.9 ± 8.4
	Median (Q1,Q3)	43.2 (35.9, 48.2)	45.2 (39.3, 51.3)
	Min,Max	18.7, 59.6	19.8, 60.7
Q1=First quartile, Q3= Third quartile, MVO=microvascular obstruction.			

*MVO and Area at Risk not collected at 30 day time point per protocol

Propensity-Matched Comparison between IC-HOT and INFUSE-AMI

The IC-HOT study pre-specified that cardiac MRI-derived infarct size data be compared to results obtained in propensity-matched INFUSE-AMI control subjects. The analysis included 52 subjects with 4-day MRI scans and 78 subjects with 30-day cardiac MRI scans from INFUSE-AMI who were matched to IC-HOT subjects. Methodology for the propensity matching was not pre-specified, and covariate imbalances may exist within the analysis. In addition, lack of area at risk data for INFUSE-AMI is a limitation. Results for the comparison of infarct size are shown in **Table 19.** This pre-specified comparison failed to demonstrate, at either time point, a reduction in median or mean percent of infarct mass of myocardial mass when using adjunctive SSO_2.

Table 19. MRI Analysis at 4 and 30 Days: Propensity Score Matched Comparison between IC-HOT and INFUSE-AMI

Parameter	Statistics	4 day IC-HOT	4 day INFUSE-AMI	30 day IC-HOT	30 day INFUSE-AMI
% of Infarct Mass of Myocardial Mass	N	52	52	78	78
	Mean ± (StdDev)	23.6 ± 13.9	23.1 ± 12.0	19.0 ± 12.2	17.3 ± 11.3
	Median (Q1,Q3)	24.6 (13.9, 30.8)	23.0 (17.3, 30.0)	19.1 (8.8, 28.9)	18.6 (8.1, 26.7)
	Min,Max	0.0, 54.1	0.0, 49.2	0.0, 42.2	0.0, 42.8

Changes in Left Ventricular Volumes, EF over 30 Days

The IC-HOT left ventricular changes over 30 days are displayed in **Table 20** for patients with measurable scan data from both the day 4 and day 30 time points. Results are shown for all available data for day 4, day 30, and the per-patient changes from day 4 to day 30. Data were obtained for n=79 subjects who had two readable scans. The median (Q1, Q3) changes over 30 days in EDV (ml) and ESV (ml) were -2.0 (-16.0, 9.0) and -7.6 (-16.9, 1.4), respectively, representing changes of -1.1% and -8.1%. Median results for IC-HOT subjects demonstrated a reduction in left ventricular volume over 30 days and no remodeling.

Ejection fraction results are also presented in **Table 20**, showing a median (Q1, Q3) EF recovery from day 4 to day 30 of +3.4%, with a 30-day median (Q1, Q3) EF (%) of 45.2 (39.3, 51.3) (see **Table 18**).

Table 20. IC-HOT MRI Changes from 4 Days to 30 Days

Parameter	Statistics	4 Days (N=83)	30 Days (N=83)	Difference
Time from Index Procedure (day)	N	83	83	83
	Mean ± (StdDev)	4.0 ± 1.3	33.3 ± 12.3	29.3 ± 12.2
	Median (Q1,Q3)	4.0 (3.0, 5.0)	30.0 (29.0, 34.0)	27.0 (24.0, 30.0)
	Min,Max	1.0, 7.0	23.0, 113.0	18.0, 107.0
Left Ventricular End Diastolic Volume (LVEDV) (ml)	N	79	79	79
	Mean ± (StdDev)	170.7 ± 45.7	167.9 ± 42.7	-2.8 ± 19.0
	Median (Q1,Q3)	168.0 (140.0, 188.0)	161.0 (136.0, 194.0)	-2.0 (-16.0, 9.0)
	Min,Max	75.5, 331.0	88.7, 308.0	-47.0, 43.0
Left Ventricular End Systolic Volume (LVESV) (ml)	N	79	79	79
	Mean ± (StdDev)	101.1 ± 36.8	93.0 ± 34.0	-8.1 ± 14.5
	Median (Q1,Q3)	94.0 (74.1, 115.0)	87.2 (71.0, 108.0)	-7.6 (-16.9, 1.4)
	Min,Max	37.4, 261.0	40.6, 247.0	-58.0, 27.0

Parameter	Statistics	4 Days (N=83)	30 Days (N=83)	Difference
Left Ventricular End Diastolic Volume Index (LVEDVI) (ml/m^2)	N	79	79	79
	Mean ± (StdDev)	82.4 ± 19.1	81.3 ± 19.0	-1.1 ± 8.9
	Median (Q1,Q3)	79.7 (70.6, 91.1)	78.1 (67.5, 90.8)	-1.1 (-7.3, 4.5)
	Min,Max	46.0, 150.2	45.8, 139.7	-18.5, 20.1
Left Ventricular End Systolic Volume Index (LVESVI) (ml/m^2)	N	79	79	79
	Mean ± (StdDev)	48.8 ± 16.4	45.1 ± 16.0	-3.7 ± 6.8
	Median (Q1,Q3)	46.1 (37.4, 55.2)	40.6 (35.6, 52.0)	-3.6 (-8.7, 0.9)
	Min,Max	22.8, 118.4	22.2, 112.1	-26.3, 16.6
Left Ventricular Ejection Fraction (%)	N	79	79	79
	Mean ± (StdDev)	41.6 ± 8.5	45.5 ± 8.2	3.9 ± 5.1
	Median (Q1,Q3)	42.9 (35.6, 48.7)	46.2 (39.6, 51.4)	3.4 (-0.6, 7.6)
	Min,Max	18.7, 59.6	19.8, 60.7	-6.2, 16.5

Summary of Supplemental Clinical Information

AMIHOT I Clinical Trial

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.

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 worse than an 8% absolute 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 test superiority of the investigational device group compared to the control group:

- 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.

- 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 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.

Several patient subsets were pre-specified in the AMIHOT I protocol for analysis, although the trial was insufficiently powered to test these subgroup statistical comparisons in a decisive way.

The primary safety endpoint was defined as the rate of Major Adverse Cardiac Events (MACE), comprising the hierarchical total incidences of death, reinfarction, target vessel revascularization, and stroke within one month (30 days) of enrollment. A non-inferiority hypothesis with a margin of 8% was pre-specified for the primary safety endpoint.

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.

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 in **Tables 21** and **22** reveals no clinically significant differences for these patients.

Table 21. AMIHOT I Baseline Patient Characteristics

	Control Group (n=135)	**SSO_2 Therapy Group** (n=134)
Age (yrs) (mean ± SD)	60±12	60±13
Gender:		
Male	99 (73.3%)	98 (73.1%)
Female	36 (26.7%)	36 (26.9%)
Hypertension	66 (48.9%)	71 (53.0%)
Diabetes	15 (11.1%)	17 (12.7%)
Peripheral vascular disease	3 (2.2%)	3 (2.3%)

	Control Group (n=135)	**SSO_2 Therapy Group** (n=134)
Previous MI	14 (10.4%)	19 (14.2%)
Previous PCI	10 (7.4%)	16 (11.9%)
Previous CABG	2 (1.5%)	2 (1.5%)
Current smoker	57 (42.2%)	58 (43.3%)
Hyperlipidemia	56 (45.5%)	65 (54.6%)
Rescue PCI	21 (15.6%)	15 (11.2%)
Door-to-balloon time (median) (min)	90	91
Time to reperfusion (median) (min)	248	260

Table 22. AMIHOT I Baseline Patient Clinical Characteristics

	Control Group (n=135)	**SSO_2 Therapy Group** (n=134)
PCI with stenting performed	135 (100%)	134 (100%)
Infarct-related artery		
Left anterior descending coronary artery (LAD)	76 (56.3%)	81 (60.4%)
Right coronary artery (RCA)	48 (35.6%)	42 (31.3%)
Circumflex artery (CX)	8 (5.9%)	10 (7.5%)
Other	3 (2.2%)	1 (0.7%)
Lesion characteristics:		
Ostial	5 (3.7%)	2 (1.5%)
Thrombus	80 (59.3%)	93 (69.4%)
Moderate/heavy calcification	8 (5.9%)	11 (8.2%)
Chronic total occlusion	7 (5.2%)	1 (0.7%)
Initial TIMI flow grade (pre-PCI)		
0	102 (75.6%)	101 (75.4%)
I	19 (14.1%)	16 (11.9%)
II	14 (10.4%)	17 (12.4%)
III*	0 (0.0%)	0 (0.0%)
Final TIMI flow grade (post-PCI)		
0	0 (0.0%)	0 (0.0%)
I	0 (0.0%)	0 (0.0%)
II	11 (8.1%)	5 (3.7%)
III	124 (91.9%)	129 (96.3%)
GLYCOPROTEIN IIB/IIIA INHIBITOR	114 (84.4%)	120 (89.6%)

*Initial TIMI flow grade = III was excluded by protocol

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, 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 this Control population.

AMIHOT I infarct size results are expressed as a percentage of the left ventricle, shown in **Table 23**.

Table 23. AMIHOT I Infarct Size Results (%LV as measured by Tc-99m SPECT imaging)

	Control Group (median±IQR) (n)	**SSO_2 Therapy Group** (median±IQR) (n)	**p value** (Wilcoxon rank-sum test) one-sided
All infarct locations			
0-24 hrs to reperfusion	13.0 ± 26.25 (122)	11.0 ± 27.5 (121)	0.29
0-6 hrs to reperfusion	14.0 ± 26.0 (87)	7.0 ± 21.5 (81)	
Anterior MI			
0-6 hrs to reperfusion	23.0 ± 33.0 (52)	9.0 ± 30.5 (49)	

*IQR = Interquartile range

The all-patient < 24-hour group showed a favorable trend toward the SSO_2 Therapy group, with a 2% absolute reduction in median infarct size, from 13% for Control subjects to 11% in the SSO_2 Therapy group (p=0.29). *S*ubgroup analyses revealed that among anterior STEMI subjects treated within 6 hours of symptom onset, the SSO_2 Therapy group exhibited a 9% median infarct size compared to a 23% median infarct size in the Control group.

Effectiveness results for the other two co-primary endpoints (regional wall motion score index improvement, ST area reduction) in the AMIHOT I trial are shown in **Tables 24** and **25**.

Table 24. AMIHOT I Regional Wall Motion Score Index (RWMSI) Improvement Results (change in RWMSI from Baseline – 90 days; negative change = improvement)

ΔRWMSI	**Control Group** (mean ± SD) (n)	**SSO_2 Therapy Group** (mean ± SD) (n)	**p value** (t-test) one-sided
All infarct locations			
0-24 hrs to reperfusion	-0.57 ± 0.48 (119)	-0.62 ± 0.53 (115)	0.24
0-6 hrs to reperfusion	-0.56 ± 0.48 (84)	-0.69 ± 0.55 (79)	
Anterior MI			
0-6 hrs to reperfusion	-0.54 ± 0.49 (49)	-0.75 ± 0.57 (49)	

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, p=0.24); subgroup analyses suggested a larger treatment effect when the anterior $\leq$ 6 hr population was examined (-0.75 vs. –0.54 for SSO_2 and Controls). Results show greater improvement in contractility and muscle recovery in the SSO_2 Therapy group as compared with Control subjects. The observed differences in infarct size between SSO_2 Therapy subjects and Controls is greatest in the $\leq$ 6 hr anterior patient subgroup.

Table 25. AMIHOT I ST- Deviation Time Trend Curve Area Data: 0 – 3 hrs post-PCI

	Control Group median (95% CI) (n)	**SSO_2 Therapy Group** median (95% CI) (n)	**p value** (Wilcoxon rank-sum test) one-sided
All infarct locations			
0-24 hrs to reperfusion	0 (0, 34) (117)	0 (0, 186) (120)	0.5
0-6 hrs to reperfusion	0 (0, 34) (83)	0 (0, 132) (75)	
Anterior MI			
0-6 hrs to reperfusion	311 (0, 972) (46)	0 (0, 222) (46)	

ST-segment area reduction, believed to represent the continuing ischemic burden in the post-acute phase, were similar in the study arms (median ST area = 0 μV-min for both groups, p=0.5) and a difference was noted in the anterior $\leq$ 6 hr subgroup (median areas = 0 vs. 311 μV-min for SSO_2 and Controls).

The composite primary endpoint was the rate of Major Adverse Cardiac Events (MACE) at 30 days (**Table 26**). MACE includes the combined incidence of death, reinfarction, target vessel

revascularization, and stroke. A total of 9/134 (6.7%) subjects in the SSO_2 Therapy group and 7/135 (5.2%) subjects in the Control group experienced MACE.

Table 26. AMIHOT I 30-day MACE Safety Data

Group	Death	Reinfarction	Target Vessel Revascularization	Stroke	Composite MACE
SSO_2 Therapy (n = 134)	4 (3.0%)	3 (2.2%)	3 (2.2%)	1 (0.7%)	9 (6.7%)
Control (n = 135)	2 (1.5%)	3 (2.2%)	3 (2.2%)	2 (1.5%)	7 (5.2%)

The results for the entire population did not demonstrate statistical superiority for effectiveness as defined by the three co-primary endpoints. However, the anterior AMI $\leq$ 6 hr patient subgroup exhibited improvements in SSO_2 subjects for all three effectiveness endpoints.

Conclusions Drawn from the Clinical Studies

The AMIHOT II study was a prospective, randomized evaluation of the safety and effectiveness of the adjunctive use of SSO_2 Therapy administered to high-risk anterior acute myocardial infarction patients in the cardiac catheterization laboratory post-PCI, when compared to a Control group receiving the standard of care alone, PCI with stenting. Among these high-risk anterior AMI patients administered PCI within six hours of symptom onset, the administration of SSO_2 Therapy demonstrated a reduction in infarct size and met the trial's safety endpoint of non-inferiority in observed 30-day Major Adverse Cardiac Events.

The objective of the IC-HOT clinical trial was to collect confirmatory data supporting the safety and effectiveness of SSO_2 Therapy in the treatment of anterior acute myocardial infarction (AMI) patients who have undergone successful percutaneous coronary intervention (PCI) with stenting within six hours of experiencing AMI symptoms. The study was primarily focused on safety, utilizing a composite endpoint of 30-day Net Adverse Clinical Events (NACE). In addition, events of interest and associated thresholds included death (3.0%), myocardial rupture (1.0%), stent thrombosis (3.0%), and bleeding (3.0%). A maximum observed event rate of 10.7% was established based on a contemporary PCI trial of comparable anterior wall STEMI patients. The IC-HOT trial exhibited a 7.1% observed NACE rate, meeting the study endpoint. Notably, no 30-day mortalities were observed, and the type and frequency of 30-day adverse events occurred at similar or lower rates than in contemporary STEMI studies of PCI-treated patients with anterior AMI. In addition, there was no incidence of 30-day myocardial rupture, a 1.0% (1/98) observed incidence of stent thrombosis, and a 4.1% observed incidence of TIMI Minor bleeding. The IC-HOT study was not designed to demonstrate therapeutic effectiveness, which was established in the prior randomized AMIHOT II study. The IC-HOT study supported the conclusions of effectiveness established in AMIHOT II, through the collection of cardiac MRI data at day 4 and day 30. Notable measures include day 4 microvascular obstruction (MVO), which has been shown to be an independent predictor of outcomes, day 4 and day 30 left ventricular end diastolic and end systolic volumes, and day 30 infarct size. In conclusion, these clinical data continue to demonstrate the safety and effectiveness of SSO_2 Therapy for its intended population when used in accordance with its instructions for use.

Patients with anterior AMI have inherently large infarct sizes and high mortality, and no other therapy has been shown to reduce infarct size in this high-risk cohort, representing a major unmet clinical need. Through multiple clinical studies, SSO_2 Therapy administration has demonstrated infarct size reduction and no unique risks associated with either new adverse events, or an increased risk of adverse events, as compared to qualifying anterior <6 hr STEMI patients receiving primary PCI alone. The risk-benefit analysis is in favor of administering adjunctive SSO_2 Therapy to this population.

Directions For Use

Patient Anticoagulation

WARNING: Provide adequate anticoagulation prior to and during therapy per clinical practice standards.

Patient anticoagulation throughout the SSO_2 Therapy procedure is aligned with current practice in STEMI patients treated with primary PCI as outlined below. Bivalirudin is recommended for this study, but patient anticoagulation must consist of one of the following regimens:

- Bivalirudin and cangrelor, with provisional (bail-out) use of GP IIb/IIIa inhibitors allowed
- Bivalirudin, with provisional (bail-out) use of GP IIb/IIIa inhibitors allowed
- Heparin and cangrelor, with provisional (bail-out) use of GP IIb/IIIa inhibitors allowed
- Heparin and routine use of GP IIb/IIIa inhibitors

Procedural anticoagulation must consist of either bivalirudin with or without the addition of cangrelor (in which case GPIIb/IIIa inhibition is not recommended unless required for refractory procedural thrombotic complications) or heparin with either cangrelor or with routine use of a GP IIb/IIIa inhibitor. If a GP IIb/IIIa inhibitor is used, it should be continued during the SSO_2 infusion and for a total of at least 12 hours post procedure, as per standard of care. Intravenous cangrelor may also be used according to label per physician discretion, administered as a bolus plus infusion, with the infusion continued for 2-4 hours post-PCI.

If unfractionated heparin is selected, local dosing regimens may be used, although it is recommended that an initial bolus of 60 IU/kg is administered, followed by titration to the ACT of 200-250 seconds in patients receiving a GP IIb/IIIa inhibitor.

If bivalirudin is selected as the procedural anticoagulant, it should be administered as a bolus of 0.75 mg/kg IV prior to PCI, followed by an infusion of 1.75 mg/kg/h initiated as soon as possible. Intravenous cangrelor may also be used according to label per physician discretion, administered as a bolus plus infusion, with the infusion continued for 2-4 hours post-PCI.

SSO_2 Therapy Preparation (Post-PCI)

WARNING: Use aseptic technique throughout procedure.

Only physicians who have received appropriate training in the use of the DownStream System should perform SuperSaturated Oxygen Therapy (SSO_2 Therapy).

SSO_2 Therapy must be performed in the cardiac catheterization laboratory (cath lab). The patient must not be moved while the catheter is in place.

The DownStream System may not be operated concomitantly with magnetic resonance imaging.

The following devices and conditions should be in place prior to starting SSO_2 Therapy:

- Use recommended guidewire to place SSO2 Catheter.
- For a coaxial (single access site) femoral approach (Figure 4a), place the 7F Merit Medical Custom Sheath Introducer or an 8F introducer sheath with sidearm in the femoral artery.
- For a dual femoral access site, a 5F introducer sheath placed in the contralateral femoral artery is required for blood withdrawal.
- For radial access site approach (Figure 4b), place SSO2 Catheter through radial sheath introducer. An additional 5F introducer sheath in femoral artery is required for blood withdrawal.

  WARNING: **Ipsilateral insertion of a second sheath in a single femoral artery for SuperSaturated Oxygen Therapy is strictly contraindicated.**

  Precaution: The index PCI procedure may be done using femoral or radial access; the SSO_2 Therapy blood draw requires a femoral arterial access site.

  Precaution: If the recommended 7F Merit Medical Custom Sheath Introducer is not used, or less than an 8F introducer sheath (coaxial approach) or 5F introducer sheath (dual site approach) is used for femoral access, SSO_2 Therapy may stop due to inadequate flow rate.
- Post PCI, draw an arterial blood sample and analyze pO_2. Systemic arterial pO_2 must be greater than or equal to 10.7 kPa or 80 mmHg to proceed with SSO_2 Therapy.

Prepare the System for Use

1. Position the system and immobilize the wheels by pressing down on and securing the wheel locks. Ensure that the system is plugged into an electrical outlet.
2. Locate the IV pole on the top of the system. Loosen the nut of the IV Pole and slowly raise it to the desired height or until it stops. Tighten the nut to keep it in position. Hang a one-liter bag of sterile physiologic 0.9% normal saline on the system IV pole.
3. To turn on the system, rotate the green power lever handle from the Standby position until it latches into the ON position (see **Figure 5**). Engaging the power lever will simultaneously open the oxygen bottle located at the back of the system.

Figure 5. Turning on the DownStream® System

4. Confirm that the oxygen bottle contains at least 800 psig (54.4 bar) of oxygen.

   Precaution: Do not use the system if the oxygen bottle pressure is less than 800 psig (54.4 bar).

After the system is turned on, the system will start the display. When completed (this will take up to one minute), the display will change to a splash screen (**Figure 6**); indicating the system is ready for use.

Figure 6. Splash Screen

After approximately 15 seconds the screen shown in **Figure 7** appears:

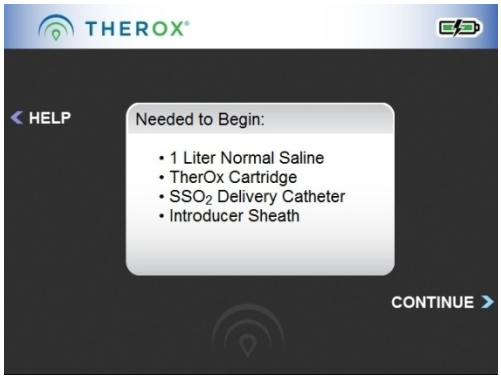


Figure 7. Screen Displays Items Required to Begin Therapy

Load the Cartridge

WARNING: Inspect the DownStream Cartridge and packaging for damage prior to use. Do not use if the cartridge or packaging is damaged.

Prior to use, all packaging, cartridge and lines should be examined for damage. Do not use any defective equipment. Contact TherOx Customer Service for replacement.

1. Open the package. Pass the cartridge tray with tube set to the sterile field.
2. A user in the sterile field removes the cartridge from the tray, keeps the sterile pouch with tube set and passes cartridge to non-sterile field.
3. Press the blue button identified as 'CONTINUE' on the display pad to continue to the next screen and begin the loading process. Once the blue button is pressed the screen shown in **Figure 8** appears:

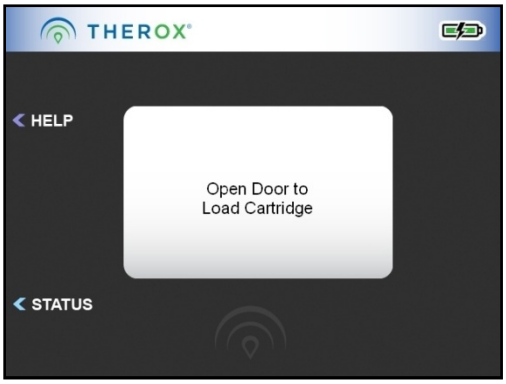


Figure 8. Screen Displays Prompt to Load Cartridge

4. Open the cartridge compartment door. A small flashing blue light in the compartment door indicates the lever for opening the door. When the door is opened, the screen will display the message, "Ready for New Cartridge".

Figure 9. DownStream Cartridge Compartment

5. Align the IV line in the open groove above the cartridge compartment (see Figure 9). Ensure the draw and return lines are placed through open grooves in the cartridge compartment.

6. Insert the cartridge, ensuring proper alignment, then close and latch the compartment door. Verify IV tube is not restricted when door is closed. Once the cartridge has been loaded and the door closed, the screen shown in **Figure 10** appears:

   Note: The blue light stops flashing.

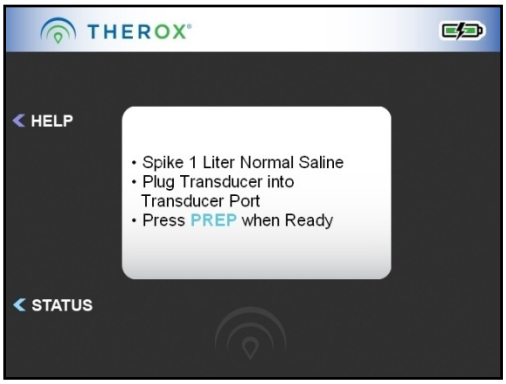


Figure 10. Prep Screen

7. Insert the IV spike into the bag of sterile physiologic 0.9% normal saline.

   WARNING: Use only 0.9% Normal saline (Isotonic solution).

8. Plug the transducer cable into the transducer port.

   Precaution: Do not expose electrical connections, including the transducer port, to fluid contact.

9. Press the blue button identified as 'PREP' on the display pad to continue to the next screen and begin the cartridge prepping process. Once the blue button is pressed the screen shown in **Figure 11** appears:

Figure 11. Prep Screen

10. Install the lines through the blood pump, flow probe, return safety clamp and return line guide while the system is in PREP (see **Figures 12** and **13**).

    a. Open the blood pump by rotating the blood pump lever upward.

b. Insert the draw line into the blood pump, aligning it with the tubing guides (V slots). After achieving proper alignment of the draw line, rotate the blood pump lever downward to close the blood pump.

Note: The blue collar on the draw line must be positioned below the pump head.

c. Press the release button for the flow probe door. The flow probe door will spring open. Insert the return line in the flow probe slot.

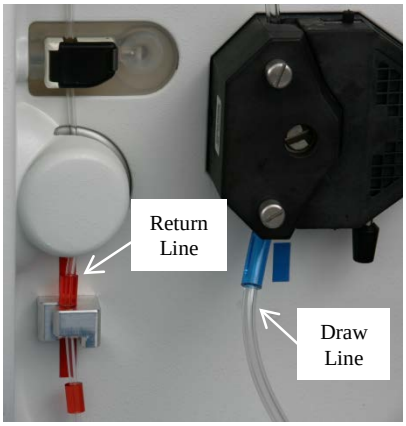
Precaution: Do not stretch the return line while loading into the flow probe.

Precaution: Ensure that the return line is fully seated in the flow probe slot before closing to prevent the flow probe door from pinching the line.

d. Close the flow probe door.

e. Insert the return line through both the return safety clamp and the return line guide.

Note: The red collars should be above and below the return line guide when properly loaded.



Figures 12. and 13. Line Installation with Close-up View

11. After the cartridge has been successfully prepped the screen shown in **Figure 14** appears prompting the operator to confirm the correct setup. If user message prompts to spike saline bag, ensure IV spike is fully inserted into saline bag, then press 'CONTINUE' to complete Prep.

Precaution: Do not unplug the transducer once the cartridge has been prepped.

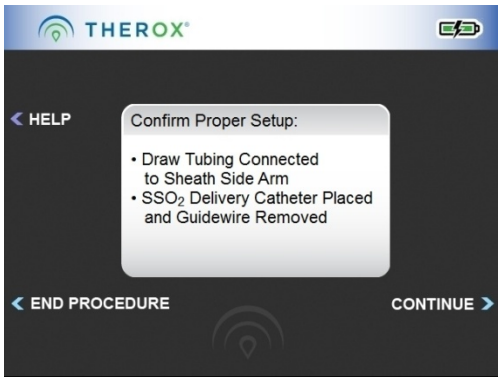


Figure 14. Proper Setup Confirmation Screen

12. After the set up has been confirmed, press the blue button identified as 'CONTINUE' on the display pad to continue to the next screen and begin the circuit priming process.

Making Patient Connections

WARNING: **Do not use any type of catheter for SSO_2 Therapy other than the SSO_2 Catheter. Inspect the SSO_2 Catheter and packaging for damage and kinking prior to use. Do not use if the catheter or packaging is damaged.**

SSO_2 Catheter Preparation

Prior to use, all packaging and devices should be examined for damage. Do not use any defective equipment. Contact TherOx Customer Service for replacement.

1. Transfer the sterile SSO_2 Catheter on to the sterile field.
2. Place the SSO_2 Catheter into the ostium of the LMCA per standard cardiac catheterization laboratory practice.
3. Remove the guidewire after satisfactory placement of SSO_2 Catheter.

   Precaution**:** After placement, inspect the SSO_2 Catheter under fluoroscopic visualization to ensure that it is seated correctly in the LMCA, and does not restrict blood flow.

4. Maintain a heparinized saline flush or lock through the SSO_2 Catheter until connection to the cartridge has been made at the end of the priming sequence.

   Precaution: Ensure fluoroscopic contrast agents delivered through the SSO_2 Catheter have been flushed prior to priming circuit; these viscous solutions may result in a flow stoppage after connection to the cartridge return line is made.

Cartridge Line Connections

Coaxial Femoral Approach – refer to **Figure 4a**

1. Release the ends of the sterile cartridge lines from the pouch on to the sterile field.
2. Attach the draw connector to the sidearm of the arterial sheath, keeping the stopcock on the sidearm closed until ready to prime the circuit with blood.
3. When ready to begin the Prime sequence, open the stopcock on the sidearm of the sheath to allow blood flow into the draw line.

Radial-Femoral Approach – refer to **Figure 4b**

1. Release the ends of the sterile cartridge lines from the pouch on to the sterile field.
2. Attach the draw line connector to the sidearm of the femoral sheath, keeping the stopcock on the sidearm closed until ready to prime the circuit with blood.
3. When ready to begin the Prime sequence, open the stopcock on the sidearm of the sheath to allow blood flow into the draw line.

Priming the Blood Path

WARNING**:** **Verify that all connections are secure and tight prior to initiating prime.**

Verify that the return line of the cartridge is NOT CONNECTED to the SSO_2 Catheter prior to initiating prime.

Precaution: Ensure that draw and return lines are not kinked or restricted prior to starting prime or at any other time during use.

1. Press and continuously hold the green PRIME button located on the system display keypad to blood prime the circuit. As the green PRIME button is held, blood will begin to flow through the circuit and out of the return line.
2. As the system pump begins to operate, a message appears on the screen indicating that the circuit is priming (see **Figure 15**). The blood pump will slow down to facilitate priming the return line.

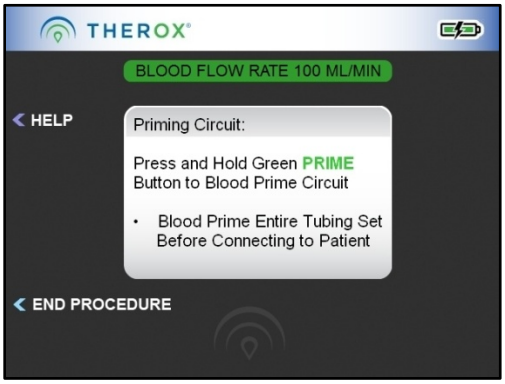


Figure 15. Prompt to Press and Hold PRIME Button

3. When the return line is blood primed and bubble free, the physician makes a wet-to-wet connection with the red return line connector to the SSO_2 Catheter hub.

WARNING: The bubble detector is disabled during prime. Ensure that return line is fully blood primed with no presence of air or bubbles in the line prior to making wet-to-wet connection to the SSO_2 Catheter.

4. Keep pressing the green PRIME button until the screen gives notice that the system pressure is stabilizing (see **Figure 16**) and allows the release of the green PRIME button.

Figure 16. Prompt to Release PRIME Button

5. At the completion of prime, visually inspect that all line connections are leak free.

WARNING: Do not disconnect return line from SSO_2 Catheter or draw line from sheath when therapy is in progress. Procedure must be stopped before disconnection.

Start and Monitor SSO_2 Therapy

Note: SSO_2 Therapy is performed in the cardiac catheterization laboratory.

1. At completion of Prime, the following screen will appear (**Figure 17**):

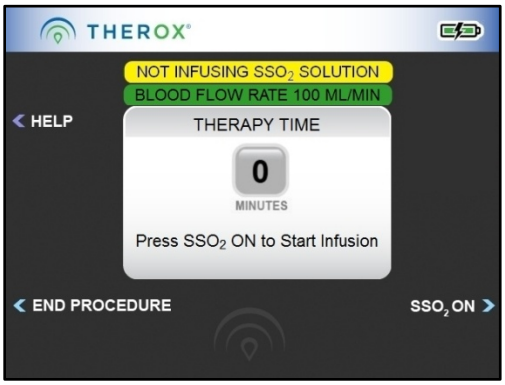


Figure 17. Screen Display for Entering SSO_2 ON

2. Press the blue button on the display keypad identified as "SSO_2 ON" to begin SSO_2 Therapy.
3. SSO_2 Therapy will continue for 60 minutes. The screen shown in **Figure 18** will be displayed during therapy.

Figure 18. Screen Display During SSO_2 Therapy

Terminate SSO_2 Therapy and Blood Flow

After 60 minutes of treatment, SSO_2 Therapy will stop and the system will indicate (on the display) that the infusion is complete. The blood pump will continue to circulate normoxic arterial blood through the cartridge; the blood will not be mixed with SSO_2 solution (see **Figure 19**).

Figure 19. Screen Display after SSO_2 Therapy Complete

1. Press the blue button identified as 'END PROCEDURE' on the display keypad.
2. The yellow message area on the screen will display a prompt to confirm the user request to end the procedure.
3. Press the blue button identified as 'END PROCEDURE' again to indicate procedure completion and to stop flow through the cartridge. The display will change to a screen that prompts the operator to disconnect from the patient and to press the blue 'CONTINUE' button when finished.

   Note: Decompression in the cartridge chamber will be accompanied by an audible hissing sound. Do not attempt to open the cartridge compartment door until prompted.
4. Once the blood pump has stopped, close the stopcock on the sheath sidearm.
5. Detach the SSO_2 Catheter from the cartridge return line by disconnecting the red return connector from the SSO_2 delivery catheter hub.
6. Disconnect the draw connector from the sheath sidearm.
7. Immediately remove the SSO_2 Catheter from the patient.

   Note: It is not recommended to return the blood in the cartridge to the patient. It is recommended to leave the blood (approximately 60 ml) in the cartridge for disposal (using standard hospital procedures to eliminate hazardous waste).

Unload the Cartridge

1. Press the blue button on the display keypad identified as 'CONTINUE' to unload the cartridge. The display will change to a screen that notifies the operator that the system is preparing to unload the cartridge (see **Figures 20** and **21**).
2. Slide the blood pump lever up toward the top of the system and remove the draw line.
3. Open the flow probe door by pressing the flow probe door release button and remove the return line.

4. Remove the return line first from the return safety clamp and then from the return line guide.

Figures 20. and 21. Prompt to Unload Cartridge

5. When the screen displays the "Open Door and Unload Cartridge" prompt, open the cartridge compartment door, unplug the transducer cable from the transducer port, and then remove the cartridge.
6. After the cartridge has been removed, close and secure the compartment door.
7. Dispose of the single-use cartridge and sterile physiologic 0.9% normal saline bag per standard hospital procedure.

WARNING: Do not re-use the single-use cartridge and SSO_2 Catheter.

Dispose of used cartridges and SSO_2 Catheters using standard hospital procedures to eliminate hazardous waste.

Shut Down the System

Move the green power lever handle from the ON position to the Standby position. This will also close the oxygen bottle located at the back of the system.

Emergency Stop

Press the large red Emergency Stop switch on the front panel, at any time, to immediately stop system operation (See **Figure 22**). To resume system use, release the Emergency Stop switch by turning it clockwise.

Note: The cartridge must be replaced to resume treatment after an Emergency Stop.

WARNING**: Under no circumstances should the extracorporeal circuit be disconnected and restarted outside the cath lab.**

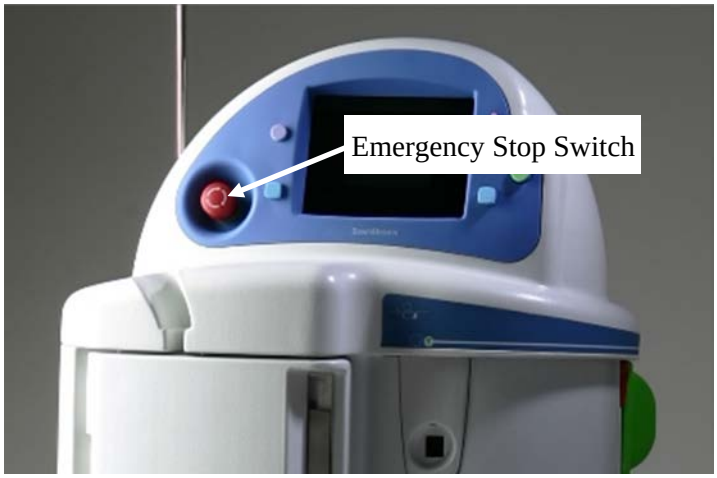


Figure 22. Emergency Stop Switch

Responding To Error Messages

Under certain conditions, an error message may appear in the message area in the center of the display screen. If the error message appears in yellow, follow the recovery procedures indicated on the screen. If the error message appears in red, the system is stopped. Follow the instructions displayed in the message area on the display.

Help Screen

The Help screen displays the TherOx Technical Support telephone number.

Equipment Maintenance - DownStream System

WARNING: Only qualified personnel trained in oxygen safety and handling should change the oxygen bottle.

- As needed, wipe the system cabinet and the interior of the cartridge compartment with an approved hospital bactericidal agent. Avoid fluid contact with the transducer port.
- To maintain batteries in fully charged condition, the system must be powered from an electrical outlet when not in use.
- After a low battery warning, allow at least six hours to fully recharge the batteries before the next use.
- Expected battery life is 200 cycles or two years.
- Systems that have been in storage (un-powered) should be charged for at least 12 hours before use.

- In normal use, a full oxygen bottle should provide over 50 uses. When the oxygen bottle contains less than 800 psig (54.4 bar), it should be replaced by qualified personnel per standard hospital procedures.
- The system contains no hospital serviceable parts.

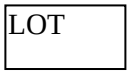
Installation and Service Requirements

Only TherOx personnel or representatives are authorized to install and service the DownStream System.

Device Labeling Symbols

Model Number

Read all instructions prior to use



Batch Code

Sterilized with ethylene oxide gas

Use By (yyyy-mm)

Do Not Reuse

Storage Temperature

Store in a cool, dry place

Cardiovascular floating defibrillation proof

~

A/C Current

A

Amps

V

Volts

Power is on

System is in standby mode, and the battery is charging (while plugged into an electrical outlet)

Fusing

Electrostatic sensitive devices

Separate collection for waste electrical and electronic equipment (WEEE)

Refer to instruction manual/booklet

Equipotentiality

Manufacturer

TherOx, Inc
17500 Cartwright Rd., Suite 100
Irvine, CA 92614-5846
USA

Rev.	DCO	Description of Change	*Check*	*Date*
A	Release per DCO 1950	*Initial release*	J.Kay	11-7-11
B	Revise per DCO 1961	*Change reference to guidewire size from .014 to .038 max. Emphasize pO_2 requirement for SSO_2 therapy.*	J.Kay	12/12/11
C	Revise per DCO 2008	*Update to reflect current 60 minute treatment parameters*	KH	04/19/12
D	Revise per DCO 2251	*Add Figure 4, anticoagulation detail, Merit sheath.* *Change TIMI II to TIMI III for patient selection.*	J. Kay	10/14/14
E	Revise per DCO 2272	*Added cangrelor to anticoagulation options, included post PCI TIMI II for patient selection, added radial option to delivery instructions.*	J. Kay	9/10/15
F	Revise per DCO 2281	*Add myocardial rupture to potential adverse events*	J. Kay	10/19/15
G	Revise per DCO 2360	*Remove Figure 4, add Figure 4a and 4b with additional description of how to set up femoral approach and radial approach for SSO_2 delivery catheter placement for therapy delivery*	J. Kay	8/4/17
H	Pending			