SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I.   GENERAL INFORMATION

Device Generic Name: SuperSaturated Oxygen Therapy

Device Trade Name: TherOx DownStream System

Device Procode: MWG

Applicant's Name
and Address: TherOx, Inc.
  17500 Cartwright Rd.
  Suite 100
  Irvine, CA 92614

Date(s) of Panel
Recommendation: None

Premarket Approval
Application (PMA)
Number: P170027

Date of FDA Notice   April 2, 2019
of Approval:

II.   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.

III.   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 delivery 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.

IV.   WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the Therox DownStream System labeling.

V.   DEVICE DESCRIPTION

The Therox DownStream System includes three components: the re-usable electromechanical console DownStream System (Model DS-1), the single-use disposable DownStream Cartridge (Model DSC-2), and the 5F SSO_2 Catheter. These component devices are supplied by TherOx exclusively for use in delivering SSO_2 Therapy. These components work in unison to perform the processes of SSO_2 Therapy delivery and blood circulation to support hyperoxemic blood delivery. A detailed description of these components follows.

The DownStream System

The DownStream System (Model Number DS-1) is the medical electrical device (console) that controls the DownStream Cartridge and monitors performance and safety during administration of SSO_2 Therapy (see **Figure 1**). The DownStream System has a touch-screen display interface to guide the health care professional through setup and clinical operation. The system is non-sterile and has no direct patient contact. The DownStream System is intended primarily to be mains operated (AC-powered) and stationary during use, but it has handles and wheels to facilitate movement and is internally powered by a battery for operation during transport (note: the patient is not to be transported/moved while therapy is being provided). The DownStream System has several integrated subsystems mounted upon a single system chassis. The major subsystems are the Cartridge Control Subsystem (CCS), Display Subsystem (Display), Power Supply Subsystem (Power Supply), and Oxygen Supply Subsystem (Oxygen

Supply). The CCS includes a housing to control mixing and metering operations for the oxygenated saline within the DownStream Cartridge. The CCS incorporates a peristaltic blood pump to control extracorporeal circuit blood flow rate; circuit pressure and bubble detection are monitored by the CCS. The CCS also includes a safety interlock which continuously monitors parameters critical to safe system operation and can safely stop therapy if necessary. The Display is the user interface for the DownStream System. The Display includes an LCD screen for user messages, a speaker for audible feedback and a keypad for user operation. The Power Supply is the power source for all system electronics, while the Oxygen Supply provides regulated oxygen to the CCS for cartridge operation.

Figure 1. DownStream System

The DownStream Cartridge

The DownStream Cartridge (Model Number DSC-2) is a sterile, single-use device that is inserted in the DownStream System to support SSO_2 Therapy (see **Figure 2**). The DownStream Cartridge comprises the blood-contact fluid flow path together with the SSO_2 delivery catheter. The DownStream Cartridge, when controlled by the DownStream System, creates SSO_2 solution from inputs of hospital-supplied oxygen gas and sterile saline solution.   The DownStream Cartridge delivers and mixes autologous arterial blood from the patient with SSO_2 solution in a carefully designed extracorporeal circuit to create oxygen-enriched hyperoxemic blood with an elevated pO_2 level of 760 – 1240 mmHg. Because the SSO_2 solution has a high oxygen concentration, the flow rate

of SSO$_2$ solution is only 3.5 ml/min out of a total return flow rate of 100 ml/min; the fluid loading to the patient is thus minimal.

The DownStream Cartridge weighs less than one pound and is constructed primarily from injection-molded polycarbonate. The tubing material is polyvinyl chloride (PVC). The draw and return tubing have approximately 8 feet of working length. The blood priming volume of the DownStream Cartridge is approximately 60 ml. The DownStream Cartridge is individually packaged.
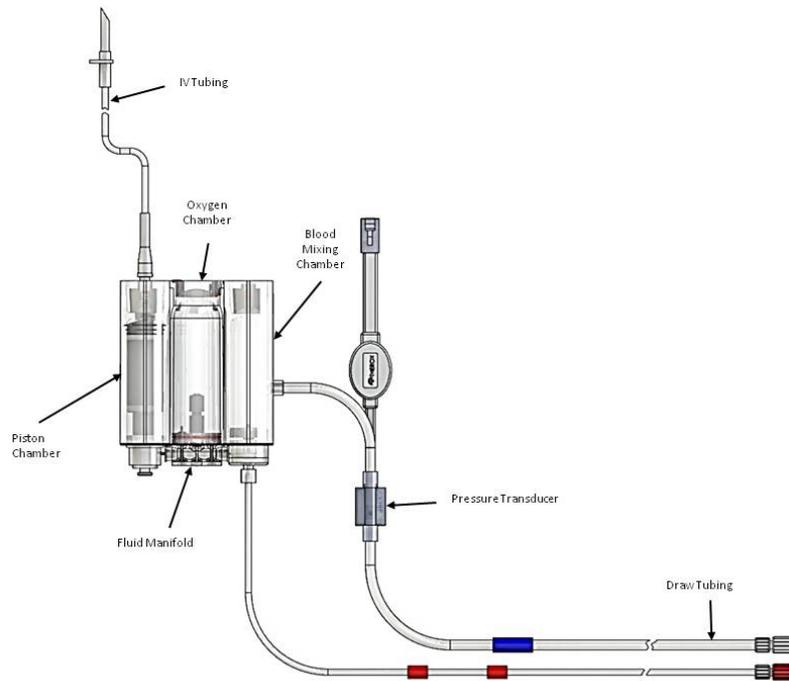

Figure 2. DownStream Cartridge

SSO$_2$ Delivery Catheter

The qualified SSO$_2$ Catheter ("catheter") is a 5F (O.D.) over-the-wire TherOx-supplied 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 been qualified by TherOx for delivery of SSO$_2$ Therapy. The catheter has a 5F outer diameter, a length of 100 cm, and a single endhole for fluid output. The catheter is provided in Judkins Left (JL) tip shapes to facilitate placement in the left main coronary ostium using a femoral or radial access site. The catheter produces a nominal circuit pressure between 1000 to 1400 mmHg at a return blood flow rate of 100 ml/min. The catheter is placed in the ostium of the left main coronary artery (LMCA) using a guidewire by the trained physician and is connected to the cartridge after blood priming. **Figure 3** shows the SSO$_2$ Catheter.
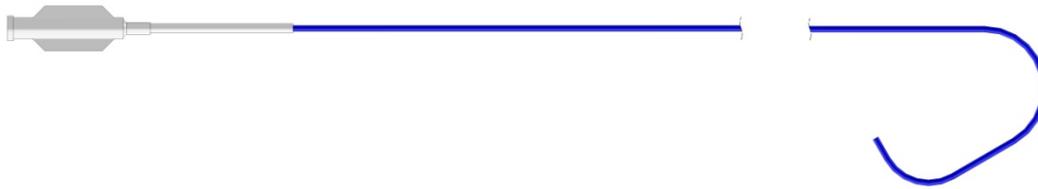
Figure 3. SSO$_2$ Catheter

Patient Connections

The DownStream Cartridge draw tubing connects to a femoral arterial sheath. This sheath may be the same sheath used for the index PCI procedure and subsequent placement of the SSO$_2$ Catheter – this is the single access site approach. For the single access site approach placement is coaxial (using one femoral arterial access site) with the catheter inserted through a 7F or larger sheath and the draw tubing hooked up to the sheath sidearm. Alternatively, a dual access site approach may be used, requiring a single 5F femoral sheath for blood withdrawal, and catheter placement through a second 5F or larger sheath placed in either the radial artery or the contralateral femoral artery. The SSO$_2$ Catheter is placed at the ostium of the left main coronary artery using standard catheterization laboratory techniques. When extracorporeal blood flow is initiated, the delivery catheter and DownStream Cartridge return tubing are wet-connected to ensure that no gaseous emboli are introduced to the patient during priming. The cartridge return tubing luer fitting connects to the luer hub of the delivery catheter.

Figure 4 provides a schematic of the patient connections during SSO$_2$ Therapy administration.
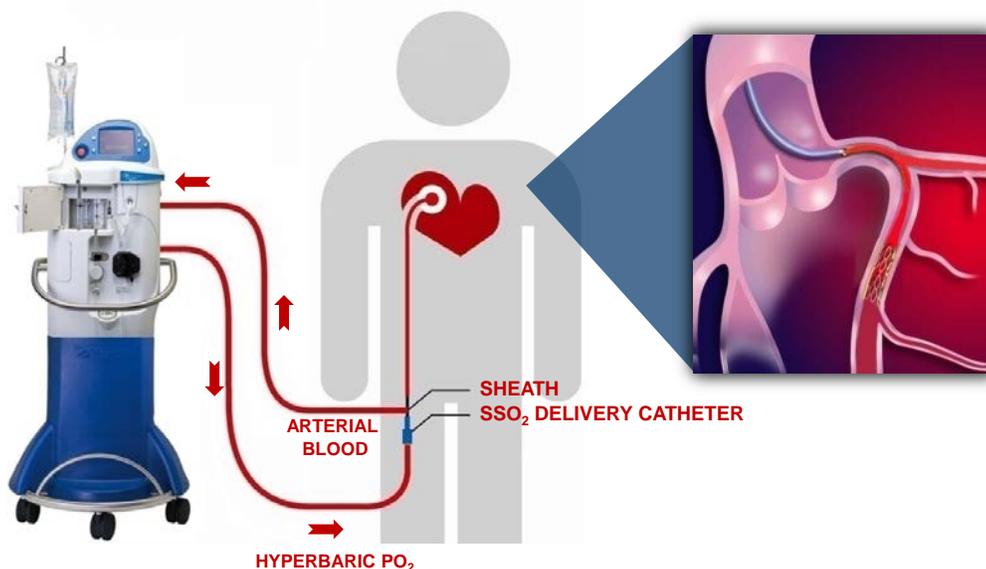

Figure 4. Patient Connections

Principle of Operation

- Hospital-supplied oxygen gas is dissolved in physiologic saline under high pressure; the resultant highly oxygenated solution is called SSO_2 solution.

- SSO_2 solution (3.5 ml/min) is combined with the autologous arterial blood (96.5 ml/min) in an extracorporeal circuit, providing hyperoxemic blood at a flow rate of 100 ml/min with an elevated pO_2 level of 1000 mmHg. A sixty-minute procedure requires 210 ml of fluid loading.

- Hyperoxemic blood is infused into the target coronary artery through the SSO_2 delivery catheter for sixty minutes. Existing patient connections, including the femoral introducer sheath, can be used for blood withdrawal and coronary access. It is also possible to place the delivery catheter using radial artery access, using femoral access for blood withdrawal.

VI.   ALTERNATIVE PRACTICES AND PROCEDURES

No available therapeutic alternatives are known for the reduction of infarct size adjunct to PCI following AMI.

VII.   MARKETING HISTORY

The TherOx® DownStream® System has not been marketed in the United States or any foreign country.

VIII.   POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Below is a list of the potential adverse effects (e.g., complications) associated with the use of the device.

- 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)

Specific adverse events that were reported in completed clinical studies of SSO_2 Therapy are presented in **Section X** below.

IX.   SUMMARY OF NONCLINICAL STUDIES

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

A. Biocompatibility

The TherOx DownStream System is the permanent hardware device component to administer SSO_2 Therapy. The system has no liquid or blood contacting surfaces. The

system operates in conjunction with two single-use disposable devices, the TherOx DownStream Cartridge and the SSO_2 Catheter.

The ISO 10993-1 standard, "Biological Evaluation of Medical Devices Part-1: Evaluation and Testing" and the FDA's Blue Book Memo G95-1 were used as guidance in selecting the appropriate tests.

Per the ISO 10993-1 standard, the DownStream Cartridge is categorized as an "External communicating device" contacting circulating blood. Duration of contact is categorized as "Limited exposure", or less than 24 hours.

Biocompatibility and toxicity testing were performed on sterile finished devices and included the following battery: Cytotoxicity, Sensitization, Intracutaneous Reactivity, Systemic Toxicity, Hemolysis, and Genotoxicity. **Table 1** provides a summary of the performed tests and corresponding document numbers. Each of these tests was conducted in compliance with Good Laboratory Practices (GLP). Results demonstrated that the DownStream Cartridge passed all required tests.

Table 1. Summary of DownStream Cartridge Biocompatibility/Toxicity Testing

Biocompatibility/Toxicity Test	Pass/Fail
Cytotoxicity	Pass
Sensitization	Pass
Intracutaneous Reactivity	Pass
Systemic Toxicity	Pass
Hemolysis	Pass
Genotoxicity	Pass
LAL Test	Pass

In addition, as part of the product sterile release system, pyrogen testing utilizing the Kinetic-Chromogenic LAL assay method has been performed for all sterilization loads with acceptable results.

Based on the results of these tests, the DownStream Cartridge materials were determined to meet the biocompatibility/toxicity requirements for the device.

B. Animal Testing

Controlled studies were performed in both porcine and canine AMI models to investigate the safety, effectiveness, and mechanism of action of SSO_2 Therapy. Key studies are summarized in **Table 2**. The findings of these studies demonstrated improved LV function, infarct size reduction, a microvascular mechanism of action, and that supersaturated oxygen therapy is non-toxic.

Table 2. Summary of Key Animal Studies

Description	Sample size	Measures	Results
Canine AMI model Post-induced AMI comparison: SSO_2 Therapy vs. autoreperfusion vs. normoxemic (pump) reperfusion (3 groups)	N=26	Myocardial blood flow (radiolabeled microspheres), left ventricular function (ECHO), ECG changes	LVEF and ECG improvement in SSO_2 group with increased microvascular blood blow compared to controls
Porcine AMI model Post-induced AMI comparison: SSO_2 Therapy vs. autoreperfusion vs. normoxic (pump) vs. pump with membrane oxygenator (4 groups)	N=59	Left ventricular function (ECHO), infarct size (histology), myeloperoxidase assays in at-risk myocardium	LVEF improvement with reduced infarct size and reduced myeloperoxidase levels in SSO_2 group compared to controls
Porcine AMI model Post-induced AMI with stenting safety comparison: SSO_2 Therapy vs. sham infusion (2 groups)	N=40	Left ventricular function, infarct size, full pathology of heart and other end organs at 7 and 28 days	LV functional improvement and smaller infarct size in SSO_2 group compared to controls with no toxicity noted in coronary arteries, myocardium, or other organs

The key summary points from animal studies are:

- SSO_2 Therapy administration post-AMI acutely improves left ventricular ejection fraction (LVEF) and regional wall motion as compared with non-treated controls.
- Control animals exhibited larger infarcts than SSO_2-treated animals as determined by post-sacrifice histological measurements of infarct size
- SSO_2 Therapy was non-toxic to the coronary arteries, myocardium, and end organs in randomized, controlled swine studies with or without induced acute myocardial infarction.
- SSO_2 Therapy administration post-AMI has exhibited regional myocardial blood flow improvement in treated animals as compared to controls.
- A significant reduction in myeloperoxidase (MPO) levels was observed in SSO_2 - treated animals versus controls; reduced MPO levels indicate improvement in underlying myocardial hypoxia.
- Transmission electron microscopy (TEM) photographs showed amelioration of endothelial cell edema and restoration of capillary patency in ischemic zone cross-sectional histological examination of SSO_2-treated animals; non-treated controls exhibit significant edema and vessel constriction at the microvascular level.

The pre-clinical animal studies conducted with the TherOx DownStream System in AMI models have demonstrated acute improvements in cardiac function and metabolic indicators of myocardial health, as well as infarct size reduction versus controls.

C. **Engineering / Bench Testing**

The DownStream System and DownStream Cartridge have undergone bench testing in support of the current SSO_2 Therapy. DownStream System bench testing includes verification of subsystems to specifications, software verification and validation testing, and validation of the integrated system to its requirements and recognized equipment standards. DownStream Cartridge bench testing includes functional testing, proof testing blood path integrity testing, performance validation in combination with the DownStream System, packaging and shelf life validation testing.

DownStream System Testing

The DownStream System hardware console was tested in accordance with its product specifications including functional and subsystem testing, software validation, and integrated performance validation testing. A summary of testing is provided in **Table 3**. The DownStream System software was verified and validated to its established requirements and complies with guidance document titled "Guidance for Industry and FDA Staff- Guidance for the Content of Pre-market Submissions for Software Contained in Medical Devices" (issued on May 11, 2005).. The software met all safety, function, and design requirements. All safety requirements identified in the Software Hazards Analysis were validated. The Display Software within the Display Subsystem and the Cartridge Control, Bubble Detector and Cartridge Interface software within the CCS successfully completed Verification and Validation (V&V) testing and the software was released for use with the DownStream System.

Validation testing was performed to demonstrate that the DownStream System Model DS-1 met its design requirements and complied with recognized equipment standards. Validation testing was conducted in compliance with Good Laboratory Practices (GLP) as outlined in 21 CFR §58. Safety, electromechanical compatibility and environmental testing were conducted by independent laboratories to recognized standards, including to IEC 60601-1, 2nd and 3rd editions and in accordance with IEC 60601-1-2 Issued: 2007 (3rd edition). The function and performance key subsystems were tested and satisfied all product requirements. The DownStream System safety response to simulated error conditions was tested and for all simulated events, the system responded in accordance with its safety requirements. SSO_2 Therapy performance validation testing demonstrated simulated clinical delivery of therapy successfully.

Based on the results from verification and validation testing, the DownStream System met established requirements and was validated to perform SSO_2 Therapy in combination with the DownStream System and SSO_2 delivery catheter.

Table 3. DownStream System Bench Test Results

Test Description	Test Article	Acceptance Criteria	Result
DownStream System Verification Testing	Cartridge Control Subsystem, Display Subsystem, Power Supply Subsystem, and Oxygen Supply Subsystem	Verification of established specifications for subsystem interfaces, functions and performance	PASS
DownStream System Software V&V Testing	Cartridge Control, Display, Cartridge Interface, Bubble Detector Software	Compliance with established software specifications and software requirements documents	PASS
Cartridge Control Subsystem Validation	DownStream System (n=3)	Compliance with Cartridge Control functional and performance requirements	PASS
Bubble Detector Subsystem Validation	DownStream System (n=3)	Compliance with Bubble Detector functional and performance requirements	PASS
Display Subsystem Validation	DownStream System (n=3)	Compliance with Display Subsystem functional and performance requirements	PASS
Power Supply Subsystem Validation	DownStream System (n=3)	Compliance with Power Supply functional and performance requirements	PASS
Oxygen Supply Subsystem Validation	DownStream System (n=3)	Compliance with Oxygen Supply functional and performance requirements	PASS
Integrated System Safety Validation Testing	DownStream System (n=3)	Compliance with DownStream System safety requirements	PASS
Integrated SSO_2 Therapy Performance Validation Testing	DownStream System (n=3)	Compliance with SSO_2 Therapy delivery performance requirements	PASS

DownStream Cartridge Validation Testing

Validation testing was performed to demonstrate that the DownStream Cartridge Model DSC-2 met its design requirements and complied with recognized equipment standards, including to IEC 60601-1, 2nd and 3rd editions and in accordance with IEC 60601-1-2 Issued: 2007 (3rd edition). Validation testing was conducted in compliance with Good Laboratory Practices (GLP) as outlined in 21 CFR §58. Tests were performed to verify the cartridge physical configuration, performance testing, non-destructive design limit testing, and proof testing. The DownStream Cartridge met established requirements and was validated to perform SSO_2 Therapy in combination with the DownStream System and SSO_2 delivery catheter. Specific test results are found in **Table 4**.

Table 4. DownStream Cartridge Bench Test Results

Test Description	Sample	Acceptance Criteria	Data	Result
Blood hemolysis testing	N=6	3-hour blood test; blood hemolysis less than 20 mg/dL/hr	Hemolysis index 7.5 mg/dL/hr average	PASS
Packaging testing of 3-year real time aged product	N=30	Peel test (1 lb min) per ASTM F88-09. Leak test per ASTM F2096-01.	All samples passed peel test and submersion leak test requirements	PASS
Blood path integrity	N=10	No leakage or failures from proof testing or pull testing of cartridge blood path. Priming volume < 100 ml	All samples had no leakage at < 60 psig, no failures at 3.3 lb, Priming volume < 100 ml (62.5 ml average)	PASS
Cycle testing at design pressure	N=10	Perform 100 flush cycles and 200 flow cycles at design pressure	All cartridges performed 100 flush cycles and 200 flow cycles at > 800 psig	PASS
Proof test at 1.5X design pressure	N=10	Two minute proof test; no damage to cartridge	All cartridges completed proof testing at 1200 psig Oxygen Chamber and 1350 psig (Piston Chamber)	PASS
Performance simulation of 3-year real time aged product	N=9	Cartridge prep in < 5 min Deliver pO2 > 760 mmHg Complete 90 minutes of circulation (1.5X duration)	Cartridge prepped in less than 5 min (90 sec average) Deliver pO2 > 760 mmHg Completed 90 minutes of therapy duration	PASS

SSO$_2$ Catheter Qualification Testing

Qualification testing was performed to demonstrate that the SSO$_2$ delivery catheter met specifications for use with SSO$_2$ Therapy. Tests were performed to verify the catheter physical configuration, catheter integrity, and performance specifications. The SSO$_2$ delivery catheter met established specifications to perform SSO$_2$ Therapy in combination with the DownStream System and DownStream Cartridge. Specific test results are found in **Table 5**.

Table 5. SSO$_2$ Catheter Bench Test Results

Test Description	Sample	Acceptance Criteria	Data	Result
Blood hemolysis testing of circuit including cartridge and catheter	N=6	3-hour blood test; blood hemolysis less than 20 mg/dL/hr	Hemolysis index 7.5 mg/dL/hr average	PASS
Catheter integrity testing	N=10	No leakage from proof testing or failure from pull testing of catheter Priming volume < 3 ml	No leakage at 100 psig No vacuum leakage No tensile failures at 3.3 lb Priming volume < 3 ml (1.3 ml average)	PASS
Performance simulation of	N=9	Deliver pO$_2$ > 760 mmHg	Deliver pO2 > 760 mmHg	PASS

Test Description	Sample	Acceptance Criteria	Data	Result
circuit including cartridge and catheter		Complete 90 minutes of circulation (1.5X duration) bubble free	Completed 90 minutes of therapy duration bubble free	

Sterilization

The DownStream Cartridge is ethylene oxide sterilized at a contracted sterilization facility. The sterilization cycle uses an Ethylene Oxide/ Carbon Dioxide gas mixture (8.5% and 91.5% respectively) with a minimum EO gas concentration of 230 mg/l. The nominal gas dwell time is 14.5 hours.

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

The SSO_2 Catheter is supplied to TherOx by the contract manufacturer pre-sterilized using Ethylene Oxide with SAL of 10^{-6} and this cycle has been qualified.

Packaging

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

The SSO_2 Catheter is pre-packaged by the contract manufacturer with five catheters provided per box in the same JL tip shape configuration. Final labeling is applied by TherOx for use of the catheter in delivering SSO_2 Therapy. The SSO_2 Catheter has a two-year shelf life.

X.   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.

A. **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 <u>not</u> 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 6** summarizes the required schedule for AMIHOT II study assessments.

Table 6. 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	♥	♥				♥					
Pre-PCI/Stent		C O N T I N U O U S	♥	♥				♥			
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										♥	

	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
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($\pm$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.

B. **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.

C. **Study Population Demographic and Baseline Characteristics**

Tables 7 and **8**, 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 7. AMIHOT II Baseline Patient Characteristics

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

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 8. 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%

	Control Group (N=79)	SSO₂ Therapy Group (N=222)
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 8 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 SSO₂ 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 SSO₂ arm. TIMI Grade 3 flow was more prevalent in the Control arm after PCI.

D. **Safety and Effectiveness Results**

a. Effectiveness

The AMIHOT II study results demonstrated superiority of SSO₂ Therapy compared to Control in median infarct size (26.5% of the left ventricular mass in the Control group; 20.0% in the SSO₂ 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 9**.

Table 9. 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 ≤ 6 hours in AMIHOT I, y = number of other subjects in AMIHOT I and z = number of subjects in AMIHOT II (all Anterior ≤ 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 10 shows the AMIHOT II infarct size results by group, and for key subgroups.

Table 10. 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

b. <u>Safety</u>

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 11**.

Table 11. AMIHOT II 30-day MACE Rates

Group	Events				Composite MACE # Patients (%)
	Death	Reinfarction	TVR	Stroke	
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 12**.

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 12**).

Table 12. AMIHOT II Overall Summary of Adjudicated Adverse Events within 30 days

Adverse Event (AE)	Randomization Group			
	Control (N=79)		SSO_2 Therapy (N=222)	
	# 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%)
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%)

	Randomization Group			
	Control (N=79)		SSO₂ Therapy (N=222)	
Adverse Event (AE)	# of Events	# (%) of Pts with Events	# of Events	# (%) of Pts with Events
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 13 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 SSO₂ Therapy group as compared to the Control group (24.3% vs. 12.7%).

Table 13. AMIHOT II 30-day Bleeding Events by Severity

Location	Bleeding Category	Adverse Event	Control (N=79) # of Events	Control (N=79) n (%) of Pts with Events	SSO$_2$ Therapy (N=222) # of Events	SSO$_2$ Therapy (N=222) 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 14)**.

Table 14. 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.

A. **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.

1. 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.

2. Follow-up Schedule

Baseline, procedural, post-procedure, in-hospital, and 30-day clinical follow-up were performed. Cardiac MRI was performed at 4 ($\pm$1) days and at 30 days ($\pm$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 15**.

Table 15. 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				√	√	√	√	√	√	√	√	√

3. <u>Clinical Endpoints</u>

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 16** below shows FDA-recommended 30-day event rate benchmarks for these individual adverse events.

Table 16. 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%

B. 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.

C. Study Population Demographics and Baseline Characteristics

The patient baseline characteristics shown in **Table 17** are consistent with an anterior STEMI population and the previously conducted AMIHOT II study.

Table 17. 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%

D. Safety and Effectiveness Results

As shown in **Table 18**, 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 18. 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 19**) 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 19. 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%)
PCI	1/98 (1.0%)
CABG	0/98 (0.0%)

Parameter	SSO₂ Therapy n/N (%) (N=100*)
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 20)** 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 SSO₂ Therapy arm and 46.8% and 19.0% for the Control arm.

Table 20. 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 21 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 21. 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%)
Unknown	0/98 (0.0%)
Myocardial Infarction	1/98 (1.0%)
Spontaneous MI	1/98 (1.0%)
Periprocedural MI - PCI	0/98 (0.0%)

Parameter	SSO$_2$ Therapy n/N(%) (N=100)
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%)
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%)

Parameter	SSO$_2$ Therapy n/N(%) (N=100)
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	
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%)

Parameter	SSO$_2$ Therapy n/N(%) (N=100)
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 22 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 22. 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 23** 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 23. 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	
% 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%)

Parameter	Statistics	Day 4 SSO$_2$ Therapy (N=88)	Day 30 SSO$_2$ Therapy (N=87)
MVO (g)	N	78	*
	Mean $\pm$ (StdDev)	2.1 $\pm$ 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 $\pm$ (StdDev)	23.8 $\pm$ 13.8	19.2 $\pm$ 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 $\pm$ (StdDev)	57.2 $\pm$ 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 $\pm$ (StdDev)	42.8 $\pm$ 24.6	
	Median (Q1,Q3)	34.4 (26.7, 57.1)	
	Min,Max	0.9, 100.0	
% of MVO of Myocardial Mass	N	78	*
	Mean $\pm$ (StdDev)	1.5 $\pm$ 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 $\pm$ (StdDev)	4.6 $\pm$ 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 $\pm$ (StdDev)	3.3 $\pm$ 4.4	
	Median (Q1,Q3)	0.9 (0.0, 5.4)	
	Min,Max	0.0, 19.4	
Left Ventricular Ejection Fraction (%)	N	86	85

Parameter	Statistics	Day 4 SSO₂ Therapy (N=88)	Day 30 SSO₂ Therapy (N=87)
	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 24.** 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 SSO₂.

Table 24. 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 25** 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 25**, 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 23**).

Table 25. 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
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

3. Pediatric Extrapolation

In this premarket application, existing clinical data was not leveraged to support approval of a pediatric patient population.

E. **Financial Disclosure**

For the AMIHOT II pivotal study:

The pivotal AMIHOT II clinical study included one hundred forty-nine (149) investigators of which zero (0) were full-time or part-time employees of the sponsor and

six (6) had disclosable financial interests/arrangements as defined in 21 CFR 54.2(a), (b), (c) and (f) and described below:

- Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0
- Significant payment of other sorts: 5
- Proprietary interest in the product tested held by the investigator: 0
- Significant equity interest held by investigator in sponsor of covered study: 4

The applicant has adequately disclosed the financial interest/arrangements with clinical investigators. Statistical analyses were conducted by FDA to determine whether the financial interests/arrangements had any impact on the clinical study outcome. The information provided does not raise any questions about the reliability of the data.

From the IC-HOT clinical study:

The IC-HOT clinical study included one hundred (100) investigators of which zero (0) were full-time or part-time employees of the sponsor and two (2) had disclosable financial interests/arrangements as defined in 21 CFR 54.2(a), (b), (c) and (f) and described below:

- Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0
- Significant payment of other sorts: 2
- Proprietary interest in the product tested held by the investigator: 0
- Significant equity interest held by investigator in sponsor of covered study: 0

The applicant has adequately disclosed the financial interest/arrangements with clinical investigators. Statistical analyses were conducted by FDA to determine whether the financial interests/arrangements had any impact on the clinical study outcome. The information provided does not raise any questions about the reliability of the data.

XI. SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION

AMIHOT I Clinical Trial

1. Background

The AMIHOT I study examined the safety and effectiveness of SSO$_2$ Therapy in both anterior and inferior STEMI patients undergoing successful reperfusion therapy via PCI up to 24 hours from symptom onset; 289 patients were enrolled in 23 investigational sites. This Phase II study, termed the Acute Myocardial Infarction with HyperOxemic Therapy, or AMIHOT I trial, was conducted from January 16, 2002 to April 3, 2004.

2. 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($\pm$7) days post PTCA/stent placement.
- Regional wall motion score index (WMSI) in the infarct zone over three months (90 $\pm$ 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.

3. 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 $\geq$ II. SSO$_2$ Therapy patients received an intracoronary 90-minute infusion of hyperoxemic blood post-PCI via infusion catheter.

4. 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 26** and **27** reveals no clinically significant differences for these patients.

Table 26. AMIHOT I Baseline Patient Characteristics

	Control Group (n=135)	SSO₂ 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%)
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 27. AMIHOT I Baseline Patient Clinical Characteristics

	Control Group (n=135)	SSO₂ 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%)

	Control Group (n=135)	SSO$_2$ Therapy Group (n=134)
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 28**.

Table 28. 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). Subgroup 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 29** and **30**.

Table 29. 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 30. 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 31**). 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 31. 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.

XII.   PANEL RECOMMENDATION

A prior PMA Submission (P080005) for the TherOx Aqueous Oxygen (AO) System, a previous device iteration of the current TherOx DownStream System and indication were presented at an FDA advisory panel held on March 18, 2009, where the AMIHOT II study was discussed. The Panel acknowledged that the AMIHOT II study met its pre-specified endpoints for safety and effectiveness, but the Panel had concerns related primarily to device safety due to a numerical increase in the observed rates of specific categories of serious adverse events that may have a causal relationship to SSO$_2$ Therapy. Therefore, the Panel recommended that additional assurance of safety be obtained through further clinical data collection for SSO$_2$ Therapy. The IC-HOT study was designed and carried out to address the Panel's concerns.

XIII.   CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

In clinical studies, the TherOx DownStream System demonstrated effectiveness in reducing infarct size when administered following primary PCI with stenting for the intended population: anterior wall STEMI patients with culprit LAD lesions who are successfully revascularized within six hours of symptom onset. Results from the pivotal AMIHOT II clinical trial demonstrated a reduction in median infarct size (% LV mass) as measured by Tc-99m sestamibi SPECT imaging from 26.5% in the Control Group to 20.0% in the SSO$_2$ Therapy Group. This infarct size reduction successfully met the study endpoint with a posterior probability of superiority of 95.1% based on an analysis of all available data using a pre-specified hierarchical Bayesian model that incorporated data from the AMIHOT I study as well. Results from the single-arm, treatment-only IC-HOT trial yielded a median infarct size of 19.4% measured by cardiac MRI; although this

reduction was not clinically different than a contemporaneous historical control cohort from INFUSE-AMI, the results are consistent with the findings of AMIHOT II

B. Safety Conclusions

The risks of the TherOx DownStream System are based on non-clinical laboratory and animal studies as well as data collected in the clinical studies. The biocompatibility and in vivo performance characteristics of the therapy provide reasonable assurance of safety and acceptability for clinical use.

The primary safety endpoint of the AMIHOT II pivotal study was the evaluation of 30-day Major Adverse Cardiac Events (MACE), including the combined incidence of death, reinfarction, target vessel revascularization, and stroke, with a non-inferiority margin of 6%. The AMIHOT II trial achieved 30-day MACE rates of 5.4% (12/222) in the SSO_2 Therapy Group and 3.8% (3/79) in the Control Group. The non-inferiority endpoint was achieved with a posterior probability of non-inferiority of 99.5% using a pre-specified hierarchical Bayesian model that incorporated data from the AMIHOT I study as well. However, concerns existed over the rates of mortality, myocardial rupture, stent thrombosis, and bleeding, each of which showed a numerically greater incidence in the SSO_2 Therapy Group compared to Control in the AMIHOT II study.

The IC-HOT study was designed to collect further data for SSO_2 Therapy and had an endpoint of 30-day Net Adverse Clinical Events (NACE), comprising the total incidence of death, reinfarction, target vessel revascularization, stent thrombosis, TIMI major or minor bleeding, and new onset severe heart failure. The IC-HOT trial met its safety endpoint with a 7.1% (7/98) observed 30-day NACE rate as compared to the pre-specified threshold of 10.7% (the observed NACE rate in the contemporary INFUSE-AMI clinical trial). The individual events of interest also met pre-specified FDA thresholds, with the exception of bleeding, though there was an absence of clinical sequalae related to the bleeding events.

The results of the pre-clinical and clinical studies of the TherOx DownStream System demonstrate that it is safe when administered for its intended use.

C. Benefit-Risk Determination

The probable benefits of the TherOx DownStream System are based on data collected in multiple clinical studies conducted to support PMA approval as described above. SSO_2 Therapy can be effective in reducing infarct size (AMIHOT-II) as compared to administering PCI with stenting alone.

The probable risks of the TherOx DownStream System include death, reinfarction, target vessel revascularization, and stroke. The TherOx DownStream System does not substantially increase the risks associated with those that exist for performing other

percutaneous coronary interventional procedures. Use of the TherOx DownStream System prolongs the total time in the cardiac catheterization laboratory by approximately one hour due to the need to perform the infusion in this controlled environment. No alternative therapies exist that offer an adjunctive benefit in reducing infarct size in this patient population.

1. Patient Perspectives

This submission did not include specific information on patient perspectives for the TherOx DownStream System.

D. **Overall Conclusions**

The data in this application support the reasonable assurance of safety and effectiveness of the TherOx DownStream System when used in accordance with the indications for use.

XIV. **CDRH DECISION**

CDRH issued an approval order on April 2, 2019. The final conditions of approval cited in the approval order are described below.

New Enrollment Study: This post-approval study is designed to confirm the safety and effectiveness of the TherOx DownStream System for use of delivery of SuperSaturated Oxygen Therapy (SSO_2 Therapy) to targeted ischemic regions of the patient's coronary vasculature in qualifying anterior acute myocardial infarction (AMI) patients who have undergone successful percutaneous coronary intervention (PCI) with stenting within six hours of experiencing AMI symptoms.

The new enrollment study is a prospective global, multicenter, randomized (1:1), confirmatory study. Patients will be randomized to either standard therapy or post-procedure infusion of SSO_2 Therapy for a duration of 60 minutes. The primary effectiveness endpoint of infarct size will be evaluated with a superiority test. The powered primary safety composite endpoint including death, stent thrombosis, major bleeding, reinfarction, new onset severe heart failure and possibly other adverse events will be developed with an appropriate non-inferiority margin. Patients will be followed for 12 months.

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

XV.   APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

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

Post-approval Requirements and Restrictions: See approval order.

XVI.   REFERENCES

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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.