

FDA Executive Summary

Prepared for the
March 18, 2009 meeting of the
Circulatory System Devices Panel

P080005
TherOx® Downstream® Aqueous Oxygen (AO) System
TherOx, Inc.

Introduction

This is the FDA Executive Summary for a first-of-a-kind device, the TherOx® Downstream® Aqueous Oxygen (AO) System (P080005). The device has been reviewed by the Division of Cardiovascular Devices within the Center for Devices and Radiological Health of the Food and Drug Administration.

This PMA assesses the safety and effectiveness of the TherOx Downstream AO System, in patients with an anterior AMI who have successful PCI within 6 hours of symptom onset. Two clinical trials (AMIHOT I and AMIHOT II) were conducted to assess the safety and effectiveness of the TherOx Downstream AO System. The AMIHOT I study was conducted in patients who had PCI within 24 hours from AMI symptom onset. This study failed to meet the prespecified effectiveness endpoint with either clinical or statistical significance; however, *post hoc* analyses identified a subset of patients from AMIHOT I who appeared to benefit from AO Therapy. This information was used to generate new hypotheses for a second study – AMIHOT II. The AMIHOT II study was conducted in patients with anterior AMI only, who received PCI within 6 hours from AMI symptom onset.

To evaluate the primary safety and effectiveness endpoints, Bayesian hierarchical modeling methodology was used by the sponsor, which allowed them to integrate data from both the AMIHOT I and AMIHOT II clinical trials.

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FDA Executive Summary Memorandum

TherOx, Inc.

P080005

TherOx® Downstream® Aqueous Oxygen (AO) System

1. PROPOSED INDICATIONS FOR USE

The TherOx® Downstream® AO System, Downstream® AO Cartridge, and MI-Cath™ Infusion Catheter are indicated for the preparation and delivery of SuperSaturated Oxygen Therapy (SSO₂ Therapy) to targeted ischemic regions of the patient's coronary vasculature immediately following revascularization by means of percutaneous coronary intervention (PCI) with stenting that has been completed within 6 hours after the onset of anterior acute myocardial infarction (AMI) symptoms.

2. DEVICE DESCRIPTION

The TherOx Downstream Aqueous Oxygen (AO) System is comprised of three major components: 1) the AO System (AOSY-1: the hardware component of the System that controls the administration of the AO Therapy); 2) the AO Cartridge (AOCR-1: Single-use disposable, three-chambered polycarbonate vessel that manufactures a continuous production of an aqueous oxygen solution from pressurized hospital-supplied oxygen and saline solution); and 3) the TherOx Infusion Catheter (MI-Cath: Single-use disposable, placed directly in the coronary artery, via the femoral artery, with the aid of fluoroscopy).

The TherOx AO System is best described as a localized hyperbaric therapy device, designed to deliver hyperoxygenated blood directly into the coronary artery supplying the site of the myocardial infarction immediately following successful PCI. The patient's own blood is extracorporeally mixed with hyperoxygenated saline solution in the AO cartridge, resulting in a pO₂ of 760-1000mmHg, and is delivered at 75 ml/min for 90 minutes. The premise behind this 90 minute treatment is that highly oxygenated blood delivered to the injured site will salvage more myocardium than in the control patients who are treated with PCI alone, and thus result in improved heart function. This study evaluated final infarct size in the patient populations by using Tc-99m sestamibi SPECT imaging at 14 days post-PCI and stent placement.

Please refer to Section 6: Downstream AO System Device Description of this panel pack (prepared by the sponsor) for further details.

3. REGULATORY HISTORY

TherOx, Inc. began their US clinical studies in January 1999 to evaluate the safety and effectiveness of the TherOx Downstream Aqueous Oxygen (AO) System in patients with acute myocardial infarction (AMI). This Study was termed the Acute Myocardial Infarction with HyperOxymic Therapy (AMIHOT I) Study. Since then, TherOx has performed a feasibility study, and two pivotal clinical studies: AMIHOT I and AMIHOT II.

The TherOx clinical investigations for the Downstream Aqueous Oxygen (AO) System began as a feasibility study in January 1999, as a multi-center (3 centers), prospective, non-randomized study design approved for 30 patients. The Pivotal phase (Phase II) of the study was approved in January 2002 for 10 sites (eventually approved for up to 22 sites) and 270 subjects, as a prospective, randomized (1:1), multi-center trial. The first AMIHOT I pivotal study patient was enrolled on January 16, 2002, with the last patient's 3-month follow-up evaluation dated April 3, 2004.

In late 2004, an analysis of the AMIHOT I study data demonstrated that the prespecified effectiveness endpoint (a co-primary endpoint including infarct size, ST-segment recovery, and wall motion score index) was not met; however, *post hoc* analyses suggested that a subset of the original patient population, i.e., anterior AMI with reperfusion \leq 6 hours of symptom onset, may benefit from AO Therapy. These findings were used to generate a new hypothesis for a second study: AMIHOT II.

The AMIHOT II study was fully approved in September 2005, for 324 subjects (304 pivotal subjects, 20 run-in patients) at 25 sites (22 of which participated in enrollment). AMIHOT II was a multi-center, prospective, randomized (2.8:1) study incorporating a Bayesian approach (to integrate prior data from the AMIHOT I study), with a revised, single primary effectiveness endpoint of reduction of infarct size as compared to the Controls (PCI/stent). Patient enrollment into AMIHOT II continued from September 2005 through May 2007. The study enrolled a total of 317 patients, including 13 run-in patients. A total of 304 patients were randomized (222 AO Therapy group, 79 Control group and 3 randomized in error, i.e., 3 were enrolled but did not meet eligibility criteria, and were not treated).

This Premarket Application (PMA) for the TherOx Downstream Aqueous Oxygen (AO) System (P080005) contains the study results from both the AMIHOT I and AMIHOT II clinical trials (using Bayesian statistical methods), evaluating the safety and effectiveness of the AO System as an adjunctive treatment of patients with anterior AMI, who received successful PCI within 6 hours from AMI symptom onset.

4. PRE-CLINICAL STUDIES

The sponsor conducted *in vitro* performance and characterization studies of the AO System:

- Test results demonstrated that the device is compliant with FDA recognized international standards for biocompatibility.
- Packaging and sterilization processes were validated according to FDA recognized international standards as well.
- FDA performed a comprehensive review of the verification and validation bench testing performed on the individual components of the AO System, as well as testing performed on the System as a whole. Studies were performed on the final product, sterilized at least 2 times, aged to an equivalent of 3 years, and tested under challenging conditions. Bench studies included 1) structural integrity of the components, bonds, joints, materials, etc.; 2) verification and validation that physical, functional, and performance attributes are within specification; 3) evaluation of all safety systems under potential fault conditions; and 4) final simulated clinical use with the entire system. The results from the bench studies supported the anticipated/intended performance of the device in the clinical environment.
- Results from software verification and validation activities provided reasonable assurance that the software in the Downstream AO System can consistently meet the specified requirements as intended.

The sponsor conducted *in vivo* performance and characterization studies of the AO System:

- As of January 2009 submission, the *in vivo* animal data on the final version of the device were incomplete with respect to adequate histopathologic assessments for thromboembolism, air bubble embolism, and oxygen toxicity. However, due to the fact that this device has been employed in > 250 patients in the combined AMIHOT I and AMIHOT II studies, FDA allowed for the provision of adequate clinical safety data to address the missing information from the *in vivo* model, and to mitigate the requirement for additional animal studies. Please refer to the Clinical Studies section of this Executive Summary memorandum for a more detailed discussion regarding stent occlusions.

Device Modification

There has been one change made to the TherOx AO System during the Phase II AMIHOT II Clinical Study. This change was the replacement of the Original Tracker-38 Infusion Catheter with the TherOx INCA-1 (now referred to as the MI-Cath) Infusion Catheter. This change was made due to the fact that the manufacturer of the Tracker-38 Infusion Catheter was discontinuing this device. The TherOx MI-Cath Infusion Catheter was designed/engineered to be very similar to the Tracker-38, and received approval to be used in the ongoing clinical trial in a letter dated June 22, 2006. The rest of the

AMIHOT II clinical study was carried out using the TherOx MI-Cath Infusion Catheter. Details regarding the similarities/differences between these two catheters can be found in the Table below:

Table 1: Descriptive Comparison of MI-Cath and TRACKER-38 Infusion Catheters

CHARACTERISTIC	MI-Cath	TRACKER-38
Outer Diameter	4.6 Fr (1.38mm) overall	5.3Fr (1.6mm) 5.0Fr (1.5mm) at tip
Inner Diameter	1.06mm overall 0.85mm minimum at marker band	1.06mm overall 0.92mm at marker band
Usable Length	127 cm	115 cm
Materials	High Density polyethylene (HDPE) shaft and luer, LDPE plasticized tip	Polypropylene/LDPE shaft, thermoplastic luer, LDPE plasticized tip

5. CLINICAL STUDIES

5.1 AMIHOT I Clinical Trial

The primary objective of the AMIHOT I study was to determine whether the adjunctive administration of AO Therapy after PCI and stenting, in a group of patients who have PCI within 24 hours from AMI symptom onset, improves left ventricular function and reduces the area of infarction. The study was conducted from January 2002 to April 2004 as a prospective, randomized (1:1), controlled, multicenter trial with 289 patients (including 20 run-in patients) enrolled at 23 centers. Patients either received PCI and stenting alone (Control group; n = 135) or PCI and stenting with adjunctive administration of AO therapy (AO therapy group; n = 134).

5.1.1 AMIHOT I – Endpoints

Safety

The primary safety endpoint was defined as the 30-day MACE rate, comprised of death, reinfarction, target vessel revascularization and stroke within 30 days of enrollment. This was a non-inferiority hypothesis with an 8% equivalence delta.

Effectiveness

The study included three co-primary effectiveness endpoints analyzed for a superiority hypothesis:

- 5% reduction in infarct size at 14 days post-PCI;
- 0.2 unit increase in Regional Wall Motion Score Index over 3 months; and
- ST segment recovery as evidenced by 50% lower ST-deviation vs. time trend curve area in the AO treatment group during the first three hours.

5.1.2 AMIHOT I – Primary Analysis

5.1.2.1 Safety

Safety data revealed no noteworthy differences in the composite 30-day MACE rate between the AO therapy and Control groups. A total of nine patients in the AO Therapy group (6.7%) and seven patients in the Control group (5.2%) experienced MACE events within 30 days of the procedure. The difference in MACE rates of 1.5% satisfied the Blackwelder’s test of non-inferiority with a safety delta of 8%. The one-sided upper 95% confidence bound, for the difference between the AO therapy and Control group MACE rate was 6.6%.

Table 2. AMIHOT I MACE

Group	Events				Composite MACE # Patients (%)
	Death	Reinfarction	TVR	Stroke	
Control (n = 135)	2	3	3	2	7 (5.2%)
AO Therapy (n = 134)	4	3	3	1	9 (6.7%)

AMIHOT I: 30-Day Deaths. There were 2 deaths in the Control group and 4 deaths in the AO group:

Control:

- Day 5. Sepsis and cardiogenic shock
- Day 0. Cardiogenic shock

AO:

- Day 0. Retroperitoneal hemorrhage. AO catheter was on same side as PCI. Adjudicated “PCI related”
- Day 9. Re-occlusion of non-target vessel stent, death
- Day 26. Cardiogenic shock (no additional information)
- Day 2. Massive anterior MI and death (AO therapy to LAD)

5.1.2.2 Effectiveness

Results for the Control/AO therapy group comparisons for the three co-primary effectiveness endpoints demonstrated a nominal improvement in the treatment group. The results did not achieve clinical or statistical significance in the entire study population. However, in *post-hoc* analyses, AO therapy seemed to compare favorably to the Control in all three co-primary endpoints in patients who were revascularized within 6 hours of AMI symptom onset and who had anterior wall infarctions (see Tables below). This anterior \leq 6 hour patient subgroup was pre-specified for subgroup analysis in the

original AMIHOT I investigational plan, but no formal hypothesis testing was pre-specified for this subgroup.

Table 3. AMIHOT I: Infarct size (%LV as measured by Tc-99m SPECT)

ITT Analysis	Median Infarct Size % (n)		p-value*
	Control	AO Therapy	
All patients ¹	13.0 (122)	11.0 (121)	0.29
Anterior MI 0-6 hrs reperfusion	23.0 (52)	9.0 (49)	0.04

¹Includes all infarct locations and 0-24 hrs to reperfusion

* Wilcoxon rank-sum test one-sided p-value

Table 4. AMIHOT I Average Infarct size (%LV as measured by Tc-99m SPECT)

ITT Analysis	Mean Infarct Size % ± SD (n)	
	Control	AO Therapy
All patients ¹	17.4 ± 16.4 (122)	16.9 ± 17.5 (121)
Anterior MI 0-6 hrs reperfusion	23.0 ± 18.9 (52)	17.3 ± 19.7 (49)

¹Includes all infarct locations and 0-24 hrs to reperfusion

Table 5. AMIHOT I: Regional Wall Motion Score Index (RWMSI)

ITT Analysis	Mean ± SD (n)		p-value*
	Control	AO Therapy	
All patients ¹	-0.57 ± 0.48 (119)	-0.62 ± 0.53 (115)	0.24
Anterior MI 0-6 hrs reperfusion	-0.54 ± 0.49 (49)	-0.75 ± 0.57 (49)	0.03

¹Includes all infarct locations and 0-24 hrs to reperfusion

* T-test one-sided p-value

Table 6. AMIHOT I: ST-Deviation Time Trend Curve Area Data 0-3 hours post-PCI

ITT Analysis	Median (n)		p-value*
	Control	AO Therapy	
All patients ¹	0 (117)	0 (120)	0.5
Anterior MI 0-6 hrs reperfusion	311 (46)	0 (46)	0.01

¹Includes all infarct locations and 0-24 hrs to reperfusion

* Wilcoxon rank-sum test one-sided p-value

AMIHOT I: Infarct Size vs. Time to Reperfusion

The following tables show that for patients with shorter time to reperfusion (0-6 hrs) there is a reduction in median (and mean) infarct size in AO therapy group compared to Control, while for subjects with 6-24 hrs to reperfusion there is an increase in median (and mean) infarct size in AO therapy group compared to Controls.

Table 7. AMIHOT I: Infarct size (%LV as measured by Tc-99m SPECT)

Anterior MI 0-6 hrs to reperfusion	Control (n=52)	AO Therapy (n=49)	Difference (Trt – Ctrl)
Mean ± SD	23.0 ± 18.9	17.3 ± 19.7	-5.7
Median	23.0	9.0	-14.0
Anterior MI 6-24 hrs to reperfusion	Control (n=18)	AO Therapy (n=24)	
Mean ± SD	19.6 ± 15.7	31.0 ± 17.6	11.4
Median	17.0	30.5	13.5
Non-Anterior MI 0-6 hrs to reperfusion	Control (n=35)	AO Therapy (n=32)	
Mean ± SD	11.2 ± 10.1	8.8 ± 9.2	-2.4
Median	10.0	5.0	-5.0
Non-Anterior MI 6-24 hrs to reperfusion	Control (n=15)	AO Therapy (n=15)	
Mean ± SD	8.7 ± 9.3	10.3 ± 8.3	1.6
Median	6.0	11.0	5.0

Given that the time to reperfusion seemed to correlate with infarct size (in the AO Therapy Group), this relationship was further examined in the AMIHOT I data by calculating the Spearman rank-correlation coefficient (ρ). In the complete data, for the AO therapy group (n=120), Spearman correlation coefficient = 0.27 (95% CI on ρ = (0.09, 0.43)) and for the Control group (n=120), Spearman correlation coefficient = 0.15 (95% CI on ρ = (-0.03, 0.32)). In the anterior \leq 6 hour patient subgroup, for the AO therapy group (n=49), the Spearman correlation coefficient = 0.12 (95% CI on ρ = (-0.17, 0.38)) and for the Control group (n=52), Spearman correlation coefficient = 0.43 (95% CI on ρ = (0.17, 0.63)).

Infarct size, one of the primary effectiveness endpoints, was also evaluated using a three-way analysis of variance model with the main effects of Time to reperfusion (0-6 vs. 6-24), Infarct location (Anterior vs. Non-Anterior) and Treatment group (AO therapy vs. Control), and incorporating time to reperfusion by treatment group interaction, infarct location by treatment group interaction and time to reperfusion by infarct location by treatment group interaction. We observe the time to reperfusion group by treatment group interaction test to be significant (F test one-sided p-value = 0.0186), while the infarct location (anterior/non-anterior) by treatment group interaction test to be not significant (F test one-sided p-value = 0.47), and infarct location by time to reperfusion

group by treatment group interaction to be also not significant (F test one-sided p-value = 0.15).

5.1.3 AMIHOT I – Conclusion

The results of the AMIHOT I study did not demonstrate overall effectiveness of the TherOx AO Therapy System in the group of patients who have PCI within 24 hours from AMI symptom onset. Results of AMIHOT I suggested possible improvement in left ventricular function and infarct size reduction in anterior AMI patients treated with PCI within 6 hours of symptom onset. The company then proposed to conduct the second trial (AMIHOT II), which focused on the limited patient cohort of anterior AMI with reperfusion ≤ 6 hours from symptom onset. A Bayesian approach was developed to integrate data from both AMIHOT I and AMIHOT II trials.

5.2 AMIHOT II Clinical Trial

The AMIHOT II Clinical Study focused on providing SuperSaturated Oxygen Therapy (AO Therapy) to targeted ischemic regions of the patient's coronary vasculature immediately following revascularization by means of percutaneous coronary intervention (PCI) after stenting has been successfully completed *within 6 hours* after the onset of *anterior acute myocardial infarction* (AMI) symptoms. The primary objective of the AMIHOT II study was to determine whether this adjunctive AO Therapy reduces the amount of left ventricular infarction with no worse than a 6% increase in incidence of MACE, when compared to a PCI/stenting alone.

Following successful PCI, patients were randomly assigned, to either the AO therapy group or the Control of PCI/stenting only with a AO therapy to Control ratio of 2.8:1. This study employed Bayesian statistical methods to integrate data from the AMIHOT I study with that of the new study. Patients were stratified on the basis of time to reperfusion (0-3 hours or >3-6 hours) and lesion location (proximal or non-proximal LAD).

5.2.1 Inclusion/Exclusion Criteria

Below is a partial list (clinically important) of the inclusion/exclusion criteria for the AMIHOT II Clinical Trial (for a complete list, please see the TherOx Executive Summary):

Pre-PCI Inclusion Criteria

- 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) 12-lead qualifying ECG criteria: Anterior infarction (ST-segment elevation > 1mm in two or more contiguous leads between V1 and V4 or new left bundle branch block (LBBB) with documentation of LAD system culprit lesion)

Angiographic Inclusion Criteria

- 5) Based on coronary anatomy, PCI is indicated for culprit lesion with anticipated use of an Intra-Coronary Stent
- 6) TIMI 0, I, or II flow is present on the initial angiographic injection of the infarct related artery
- 7) Successful angioplasty as documented by <50% diameter residual angiographic stenosis within and associated with the culprit lesion and \geq TIMI II flow and no major complications such as perforation or shock
- 8) Documented time of reperfusion is \leq 6 hours from the documented time of symptom onset

Pre-PCI Exclusion Criteria

- 1) Absolute contraindications to anticoagulant therapy, including hemorrhagic diathesis or thrombocytopenia
- 2) Systemic Arterial pO₂ is <80 mmHg with supplemental oxygen
- 3) Placement of an intra-aortic balloon pump (IABP)
- 4) Patients requiring cardiopulmonary resuscitation for >10 minutes
- 5) Cardiogenic shock (SBP <80 mmHg for more than 30 minutes unresponsive to fluids or requiring intravenous pressors or placement of an IABP)

Angiographic Exclusion Criteria

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

5.2.2 Endpoints

5.2.2.1 Primary Safety (non-inferiority)

The primary safety endpoint was a composite endpoint defined as the 30-day (or hospital discharge, whichever is longer) MACE rate, comprising death, reinfarction, target vessel revascularization, and stroke within 30 days of enrollment. The sample size calculation

was based on a literature review of acute MI trials which resulted in a predicted 30-day MACE rate of 7% in the Control patients. An equivalence delta (based on this Control rate) of 6% was prospectively agreed to for this study

The hypotheses for the primary safety endpoint in AMIHOT II were:

$$H_0: \pi_t \geq \pi_c + 6\%$$

$$H_a: \pi_t < \pi_c + 6\%, \text{ where}$$

π_t and π_c are the underlying proportion of patients having an incidence of death, reinfarction, target vessel revascularization, or stroke for treatment and control groups, respectively.

The safety endpoint was considered to have been met if there was a high posterior probability of non-inferiority [i.e. $P(\pi_t < \pi_c + 6\%) > 95\%$] in the AMIHOT II trial conditional on the safety data from both trials.

5.2.2.2 Primary Effectiveness (one-sided, Bayesian superiority)

The primary effectiveness endpoint for this study was a reduction in infarct size as measured by percent of left ventricular volume, assessed by Tc-99m Sestamibi SPECT imaging, at 14 days post-PCI/stenting.

The statistical hypotheses for the primary effectiveness endpoint in AMIHOT II were:

$$H_0: \mu_t \geq \mu_c$$

$$H_a: \mu_t < \mu_c, \text{ where}$$

μ_t and μ_c are the underlying infarct size for treatment and control groups, respectively.

The statistical hypothesis for the effectiveness endpoint was to be considered to have been met if there was high posterior probability (more than 95%) of superiority [i.e., $P(\mu_t < \mu_c) > 95\%$] in the AMIHOT II trial conditional on the effectiveness data from both trials.

5.2.2.3 Secondary Effectiveness

ST-segment recovery as measured by time trend curve areas computed at 3, 4, and 6 hours post-procedure.

5.2.3 Results

The AMIHOT II study enrolled a total of 317 patients, including 13 run-in patients (not included in final analyses). A total of 304 patients were randomized (222 AO Therapy group, 79 Control group and 3 randomized in error [3 were enrolled but did not meet eligibility criteria, and were not treated]). A total of 22 sites participated in enrollment,

with 59% (178/301) of the patients enrolled in non-US sites. All 301 treated patients (designated as ITT population) had 30-day post-procedure follow-up.

There was no imbalance in baseline characteristics between groups. This was primarily a study of white (94%) males (80%). The patients enrolled into the AMIHOT II study were a highly selected AMI group with >30 inclusion/exclusion criteria. Only 12.6% of the AMI patients screened were enrolled in the study. The following were the primary reasons for screening failure:

- Enrolled (anterior MI, <6 hrs) 12.6%
- Non-anterior MI 49.4%;
- Symptoms >6 hrs 13.5%;
- Non-qualifying anterior MI 24.5%;
 - IABP/shock 4.5%;
 - Pre-PCI TIMI 3 flow 3.6%;
 - Clinical complications 3.2%;
 - Physician discretion 3.0%;
 - Patient refusal, inability to get consent 3.0%;
 - Other 7.3%

5.2.3.1 Primary Safety Endpoint – 30-day MACE Rate

The composite safety endpoint, MACE, included death, reinfarction, target vessel revascularization (TVR), and stroke within 30 days. There were no missing values for the primary safety endpoint measure in either group. The proportion of patients who experienced a MACE event within 30 days of the procedure was 3.8% (3/79) in the Control group and 5.4% (12/222) in the AO Therapy group (Exact 95% CI for difference in MACE rates between AO therapy group and Control group = [-5.4%, 6.6%]).

Table 8. AMIHOT II MACE

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

Deaths

One of the components of the composite safety endpoint, MACE, was death within 30 days. For the AMIHOT II Study, there were four deaths (1.8%) observed in the AO therapy group compared to zero (0%) in the Control group within 30 days (Exact 95% CI for difference in death rates between AO therapy group and Control group = [-2.6%, 4.7%]):

- Day 0. Patient had ventricular tachycardia/fibrillation with cardiac arrest after 4 minutes of AO therapy; LAD and circumflex occlusions found. Adjudicated “related to AO therapy”.
- Day 4. Myocardial rupture in LAD region
- Day 9. Ventricular septal wall rupture
- Hypoxic encephalopathy pre-procedure secondary to cardiac arrest (protocol deviation of inclusion criteria).

When the same patient cohort for the AMIHOT I study is included in this rate, there were 0/131 (0%) deaths in the Control group, and 6/271 (2.2%) in the AO group (Exact 95% CI for difference in death rates between AO therapy group and Control group = [-0.5%, 4.8%]).

The one year cumulative death rate for AMIHOT II, was 1/77 (1.3%) in the Control arm and 8/220 (3.6%) in the AO therapy group.

Stent Occlusions

The infusion catheter associated with the device is generally placed inside the newly-placed stent “just at the proximal edge.” There is a theoretical possibility of the infusion catheter disrupting the target artery or the catheter decreasing flow in the target artery, thus leading to stent thrombosis and occlusion. Since the MACE endpoint of TVR does not include any revascularization that occurred in the catheterization laboratory during the initial procedure or device treatment, acute stent occlusions were not part of the primary safety endpoint. This is relevant because in the Control group, the patient would leave the catheterization laboratory after the PCI, while in the AO group they would stay for approximately 2 or more hours. In fact, one of the MACE events of TVR in the Control group occurred 1 hour after leaving the catheterization laboratory (patient number 024-205). This would not have been determined to be a MACE event in the AO group because the patient would still have been in the catheterization laboratory. Patients who had the infusion catheter placed but did not have at least 60 minutes of infusion were excluded in the Per Protocol analysis, thus missing several patients with acute stent occlusions.

The Sponsor calculated the stent occlusion rate as 4.1% (9/222) for the AO group versus 2.5% (2/79) for the Control group. According to FDA’s review, there were two additional patients listed in the SAE narratives with stent occlusions in the AO group, therefore we believe the rate is 4.9%. The Sponsor states that most of the stent occlusions have been adjudicated as not related to the device or procedure. The CEC Charter states that events were judged to be device-related only when “The clinical event has a reasonable time sequence to use of the investigational devices...” For this reason, only events occurring during use of the device were counted as device-related and the rest were attributed to the PCI. This does not account for any possibility that occlusions occurring after the catheter was removed were in fact related to the device. There was no correlation found between stent occlusions and the type of stent (bare metal vs. drug-eluting)

The two patients counted by the FDA as having stent occlusions, but not counted by the Sponsor were:

- Stent occlusion in the target artery at 24 days found “incidentally” after cardiac catheterization for symptoms due to disease in another coronary artery (patient 022-274).
- Stent occlusion in the target artery in a patient who had cardiac arrest after 4 minutes of AO therapy. The Sponsor states that “It cannot be determined if this finding was primarily related to the low flow/cardiac arrest (most likely) or primary stent occlusion (less likely secondary to no preceding new EKG changes” (patient 022-137).

There were 2 episodes of coronary spasm in the target vessels determined to be a serious adverse event – one in the AO arm and one in the AO run-in patients.

Bleeding Events

Bleeding events were more common in the AO group. This might be related to either anticoagulation or to the need for access. The AO procedure requires that heparinization be utilized during the procedure with an Activated Clotting Time kept >250 seconds, thus prolonging the time of heparinization for approximately two hours. Two catheters were used during the study; the Tracker-38 was the only catheter available for the first two thirds of the trial and the smaller MI-Cath infusion catheter was available for the last part of the trial. Two catheter configurations could be used. The first was a “coaxial” configuration where the sheath used for PCI was also used for the AO procedure. The AO procedure required a 9F sheath, which could result in the PCI sheath being upsized to 9F. When the smaller MI-Cath infusion catheter became available, a 5F or 6F sheath could be used in the contralateral femoral artery, thus obviating the need to upsize the PCI sheath. Therefore, either manipulation or upsizing of the PCI sheath or insertion of a second, contralateral sheath was needed for the AO catheter, thus increasing the opportunity for mechanical trauma to the access artery. In addition, some patients were transferred from the catheterization laboratory with the AO infusion in progress and this could have added additional mechanical stresses on the access site(s).

If one looks at the SAEs of retroperitoneal hematoma, pseudoaneurysm, and catheter site hematoma, ten AO patients ($10/222 = 4.5\%$) and two Control patients ($2/79 = 2.5\%$) experienced these complications. Five of the AO patients required transfusions of two or more units of blood; none of the Control patients required transfusion. There was a modest but statistically significant decrease in hematocrit and hemoglobin in the AO group, most likely due to blood loss in the AO cartridges as well as hemodilution. The hemoglobin was 13.6 in the Control group at 24 hours vs. 12.9% in the AO group, $p=0.0005$.

Mobile Operation of the System

The clinical protocol specified that sites could undergo training to conduct some of the perfusion out of the cardiac catheterization laboratory. Three of the 22 sites chose to transfer the patient out of the cardiac catheterization laboratory to conduct at least part of the perfusion. The majority of the patients (70.4%) had the AO intracoronary procedure completed in the catheterization laboratory while 26.9% had the intracoronary infusion completed in the CCU or cath lab holding area. Of the 2 acute stent occlusions that occurred during AO infusion at these 3 sites, one occurred in the cardiac cath lab and one occurred in a patient who was in the CCU.

It is possible that bleeding could have been caused by moving the patient from the cardiac catheterization laboratory during infusion. At the 3 sites where patients were moved, a total of 6 patients had the complications of pseudoaneurysm, catheter site hematoma, or hemorrhage. These bleeding complications occurred in 4 patients who had infusions in the CCU or holding area and 2 patients who were not moved.

5.2.3.2 Primary Effectiveness Endpoint – Infarct Size

The primary left ventricular (LV) infarct size data were evaluable for 72/79 (91.1%) Controls and 209/222 (94.1%) AO therapy patients.

The following tables further evaluate the primary effectiveness endpoint, infarct size, for all evaluable subjects. There was a **6.5%** observed reduction in median infarct size, with median infarct size of 26.5% in the Control group and 20% in the AO Therapy group. There was a **3.9%** observed reduction in mean infarct size, with mean infarct size of 27.1% in the Control group and 23.2% in the AO therapy group. Based on the pre-specified Bayesian model (**Model M1**; see Appendix II for details), using available data (evaluable patients), the results demonstrated that the primary effectiveness endpoint was successfully met, with posterior probability of superiority = 95.1%.

Based on medical literature, the sponsor prospectively referred to “a reduction in infarct size of 5% of the left ventricle as a clinically meaningful measure of [effectiveness] in such trials.” In the AMIHOT II study, the reduction in median infarct size (6.5%) was greater than 5% but the reduction in mean infarct size (3.9%) was less than 5%. The clinical significance of these results is discussed briefly below, but requires further discussion.

Table 9. AMIHOT II: Median Infarct size (%LV as measured by Tc-99m SPECT)

ITT Analysis	Median (n)		Difference (Trt – Ctrl)
	Control	AO Therapy	
All patients	26.5 (72)	20.0 (209)	-6.5

Table 10. AMIHOT II: Average Infarct size (%LV as measured by Tc-99m SPECT)

ITT Analysis	Mean \pm SD (n)		Difference (Trt – Ctrl)
	Control	AO Therapy	
All patients	27.1 \pm 19.1 (72)	23.2 \pm 19.1 (209)	-3.9

Clinical Significance of 5% Reduction in Infarct Size

It was prospectively proposed by the Sponsor, and agreed upon by the FDA, that a 5% reduction in infarct size in AO therapy group compared to Control group would be a clinically meaningfully important reduction. It was not specified whether this 5% would be calculated using the median or mean values. However, please note the following points:

- This was discussed relative to the data in AMIHOT I where the mean infarct size was presented as the co-primary effectiveness endpoint.
- The hypothesis for AMIHOT II was based on the mean, not median, reduction in infarct size.
- In the AMIHOT II Statistical Plan, the Sponsor stated that the data would be presented as means "...as well as medians..."
- Upon reviewing the literature on which the Sponsor based the concept that a 5% reduction in size was clinically important, it is clear that the various publications are divided over whether mean or median was used.

The following histograms (Figure 1) show the distribution of infarct size in the two treatment groups for all evaluable subjects. Note that the distribution has a peak at one end of the range (i.e., 0) and is otherwise reasonably flat for both Control and AO therapy groups.

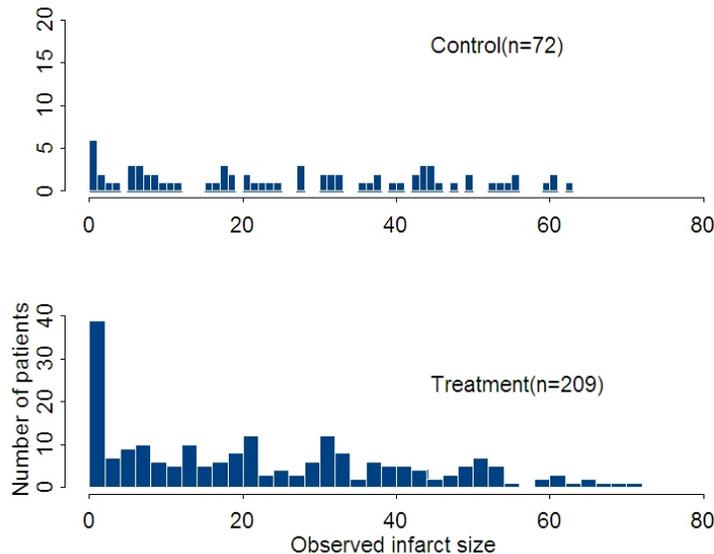


Figure 1. Histogram displaying the distribution of infarct size in the two treatment groups for AMIHOT II clinical trial.

Stratified Analysis of Infarct size by Time to Reperfusion

An exploratory analysis of AMIHOT I data led to the finding that for patients with shorter time to reperfusion (0-6 hrs) there is a reduction in median (and mean) infarct size in the AO therapy group when compared to the Controls, while for subjects with 6-24 hrs to reperfusion there is an increase in median (and mean) infarct size in the AO therapy group when compared to the Controls. The AMIHOT II data indicates, however, that while for patients with 0-3 hrs to reperfusion there is a reduction in median (and mean) infarct size in AO therapy group compared to Control, for patients with 3-6 hrs to reperfusion there is a slight increase in median (and mean) infarct size in AO therapy group compared to Controls. In addition, exploratory analysis further suggests complexity in the relationship between infarct size and time to reperfusion. These findings raise concerns as to whether 6 hours is the appropriate “cut-off” for time to reperfusion used to identify the patient population that is most likely to receive benefit from this treatment and, therefore, the population that should be specified in the indication for use.

Table 11. AMIHOT II: Infarct size (%LV as measured by Tc-99m SPECT) for patients with 0-3 hrs to reperfusion

	0-3 hrs to reperfusion		
	Control (n=41)	AO Therapy (n=88)	Difference (Trt – Ctrl)
Mean ± SD	29.6 ± 20.0	18.8 ± 18.0	-10.8
Median	32.0	14.0	-18.0

Table 12. AMIHOT II: Infarct size (%LV as measured by Tc-99m SPECT) for patients with 3-6 hrs to reperfusion

	3-6 hrs to reperfusion		
	Control (n=31)	AO Therapy (n=121)	Difference (Trt – Ctrl)
Mean ± SD	23.7 ± 17.6	26.3 ± 19.3	2.6
Median	21.0	26.0	5.0

Given that the time to reperfusion seems to correlate with infarct size (in the AO Therapy Group), this relationship was further examined by calculating the Spearman rank-correlation coefficient (ρ). For the AO therapy group, the Spearman correlation coefficient = 0.20 (95% CI on ρ = (0.065, 0.33)) and for the Control group, the Spearman correlation coefficient = -0.05 (95% CI on ρ = (-0.28, 0.18)). The positive correlation between time to reperfusion and infarct size in the AO Therapy Group suggests that shorter time from symptom onset to reperfusion is associated with smaller infarct size and longer time from symptom onset to reperfusion is associated with larger infarct size. This again raises concern about the appropriate “cut-off” for time to reperfusion.

Infarct size was also evaluated using a two-way analysis of variance model with the main effects of Time to reperfusion (0-3 vs. 3-6) and Treatment group (AO therapy vs. Control), and incorporating time to reperfusion by treatment group interaction. We observe the time to reperfusion group by treatment group interaction test to be significant (F test one-sided p-value = 0.01).

Stratified Analysis of Infarct size by Infarct Location

An exploratory analysis of the AMIHOT II infarct size study data, stratified by proximal vs. non-proximal LAD, appears to suggest a larger reduction in median infarct size in the non-proximal LAD.

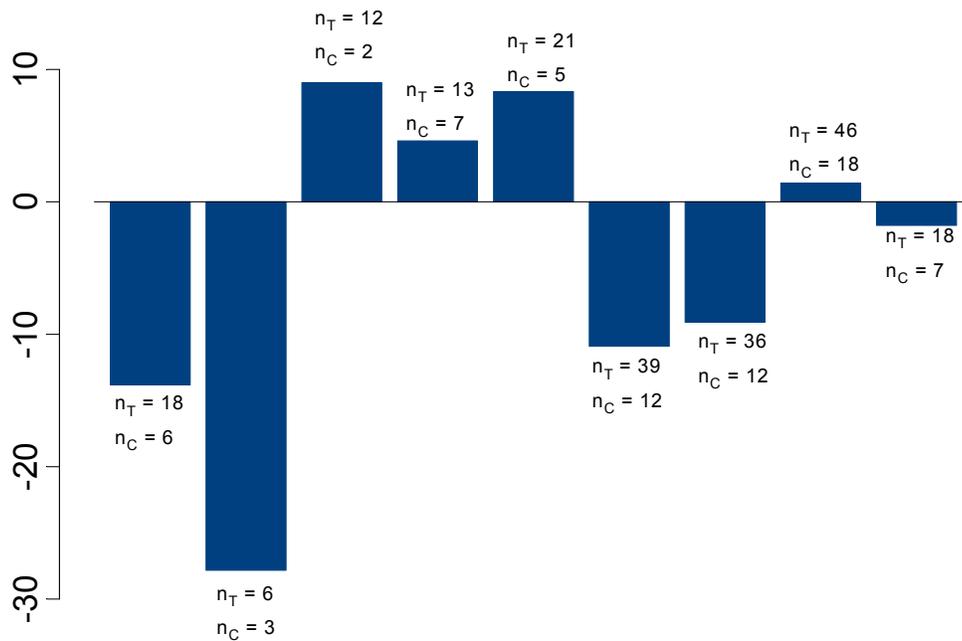
Table 13. AMIHOT II: Infarct size (%LV as measured by Tc-99m SPECT)

Infarct location	Median (n)	
	Control	AO Therapy
Proximal LAD	29.5 (34)	30 (100)
Non-proximal LAD	21.5 (38)	14 (109)

A two-way analysis of variance model was performed for infarct size, with the main effects of Infarct location (Proximal vs. Non-Proximal) and Treatment group (AO therapy vs. Control), and incorporating infarct location by treatment group interaction. We observe the infarct location by treatment group interaction test to be not significant (F test one-sided p-value = 0.19).

Center Effect on Primary Effectiveness Endpoint

In this study, patients were enrolled at 22 centers. Data from two of the centers were combined and considered as a single enrolling investigational site since patients at those two centers were enrolled under one IRB and one primary investigator. Eight centers had an enrollment of more than 10 patients. The following histogram (Figure 2) shows the treatment effect, calculated as the difference in the mean infarct size between the AO therapy and Control group, in each of the eight centers and a combined effect for the remaining small centers (the right most bar of the histogram). Note that the treatment effect ranges from -27.8% to 9.0%. In 4 of those 8 centers, there was, a reduction in mean infarct size in the AO therapy group compared to the Control group (-27.8 to -9.1%), while in the other 4 centers there was, an increase in mean infarct size in the AO therapy group compared to Control group (1.4% to 9.0%).



Treatment effect by center

Figure 2. Difference in mean infarct size between the AO Therapy and Control group by center. The right most bar represents the treatment effect in small centers combined. n_T and n_C are the number of evaluable patients by center in the AO Therapy Group and Control group, respectively.

5.2.3.3 Secondary Effectiveness Endpoint – ST-segment Recovery

The study had a prespecified secondary endpoint of ST-segment recovery by time-trend curve at 0-3 hours, 0-4 hours, and 0-6 hours. In AMIHOT I, the *post hoc* subgroup analysis showed significant improvement in the AO therapy group (median ST area during 0-3 hrs in control vs. treatment group = 311 vs. 0; Wilcoxon rank sum test one-sided p-value = 0.01). As shown in the table below, however, results from the AMIHOT II study demonstrated no observed difference in the median accumulated ST area between the AO therapy group and Control group, at any time point (0-3 hrs, 0-4 hrs, 0-6 hrs, 0-24 hrs) - the Wilcoxon rank sum test comparing treatment groups, also did not reveal any statistically significant difference:

Table 14. AMIHOT II ST Time Trend Curve Area 0-3, 0-4, 0-6, 0-24 hrs

	ST area ($\mu\text{V} - \text{min}$) (median \pm IQR)
0-3 hours	
Control (n = 75)	0 \pm 1244
AO Therapy (n = 202)	0 \pm 1270
0-4 hours	
Control (n = 73)	0 \pm 1243
AO Therapy (n = 208)	0 \pm 988
0-6 hours	
Control (n = 76)	0 \pm 1244
AO Therapy (n = 212)	0 \pm 1178
0-24 hours	
Control (n = 76)	0 \pm 1497
AO Therapy (n = 206)	0 \pm 1680

5.2.3.4 *Other Evaluations*

Laboratory Values

There was a small, statistically significant increase in serum creatinine at 24 hours in the AO group (Control 1.0 mg/dL vs 1.1 mg/dL for AO, $p=0.04$). There were no meaningful differences in CPK, CPK-MB, or Troponin between the two groups.

Hospital Stay and Stepdown Unit Stay

The AO patients remained in the hospital longer than the Control patients (5.7 days vs 4.7 days, $p=0.03$) and remained in a step-down unit longer (3.5 vs. 2.7 days, $p=0.03$), although there was no statistical difference in ICU days.

5.2.4 *Bayesian Analysis*

Bayesian hierarchical modeling methodology was employed to assess the primary safety and effectiveness endpoints (please see Appendix II for a brief discussion of Bayesian Statistics). The study success was evaluated based on AMIHOT I and AMIHOT II study results. The model was structured so that the AMIHOT I results were sub-divided into four subgroups, based on time to reperfusion (0-6 hrs, 6-24 hrs) and location (Anterior MI, Non-Anterior MI). The AMIHOT II study contained data on only group 1 (Anterior MI, 0-6 hrs to reperfusion).

5.2.4.1 *Primary Safety Endpoint – 30-day MACE Rate*

The safety endpoint was considered to have been met if there was a high posterior probability of non-inferiority [i.e., $P(\pi_t < \pi_c + 6\%) > 95\%$] in the AMIHOT II trial conditional on the safety data from both trials.

Based on the pre-specified Bayesian model (**Safety Model**; see Appendix III for details), using available data without imputation, the results demonstrated that the primary safety endpoint was successfully met. The posterior probability of non-inferiority for the safety endpoint = 99.5%. The following histogram shows the posterior distribution of the π_t , the proportion of patients having an incidence of MACE in the treatment group, minus π_c , the proportion of patients having an incidence of MACE in the Control group.

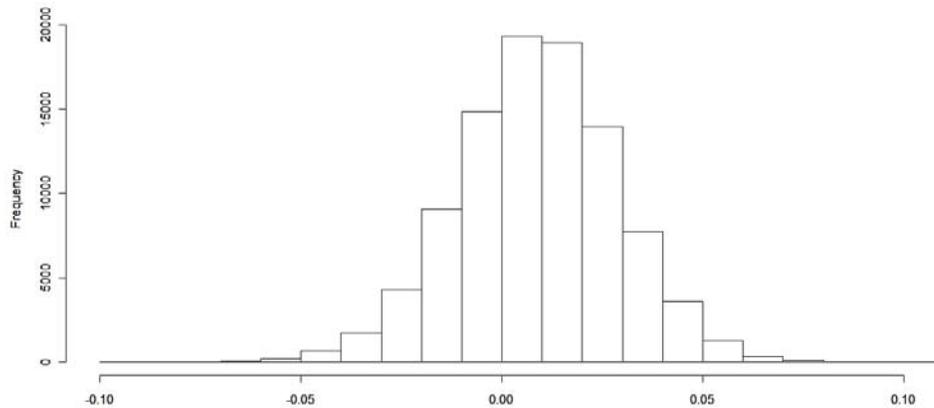


Figure 3. Posterior distribution of $(\pi_t - \pi_c)$

5.2.4.2 Primary Effectiveness Endpoint – Infarct Size

To reduce skewness of the data, the primary effectiveness endpoint, infarct size, was transformed using the form $Y = \log(X+10)$. The log-transformed values in each subgroup were assumed to be normally distributed with a mean and standard deviation specific to the subgroup-treatment (AO therapy vs. Control) combination. The effectiveness endpoint was considered to have been met if there was high posterior probability (more than 95%) of superiority [i.e., $P(\mu_t < \mu_c) > 95\%$] in the AMIHOT II trial conditional on the effectiveness data from both trials.

Based on the pre-specified Bayesian model (**Model M1**; see Appendix III for details), using available data (evaluable patients), the results demonstrated that the primary effectiveness endpoint was successfully met. The posterior probability of superiority for the effectiveness endpoint = 95.1%. The following histogram shows the posterior distribution of μ_t , the mean infarct size in the treatment group, minus μ_c , the mean infarct size in the Control group.

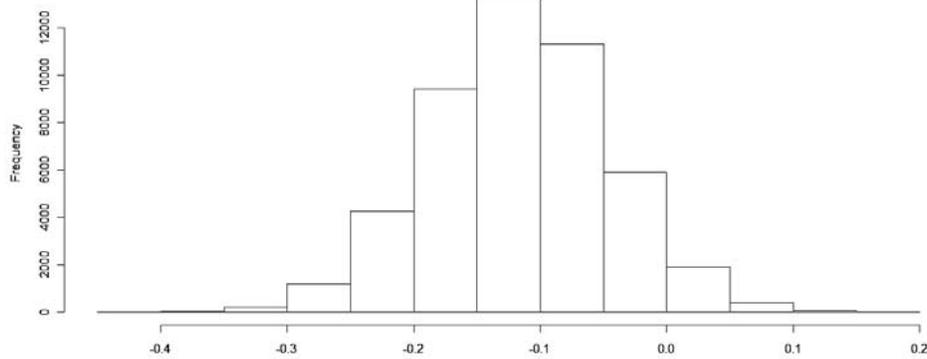


Figure 4. Posterior distribution of $(\mu_t - \mu_c)$

However, after assessing the distribution of the log-transformed infarct size in both treatment groups (see Figure 5) FDA expressed concerns about the deviation of the distribution from normality and its effects on the validity of the Bayesian analysis results.

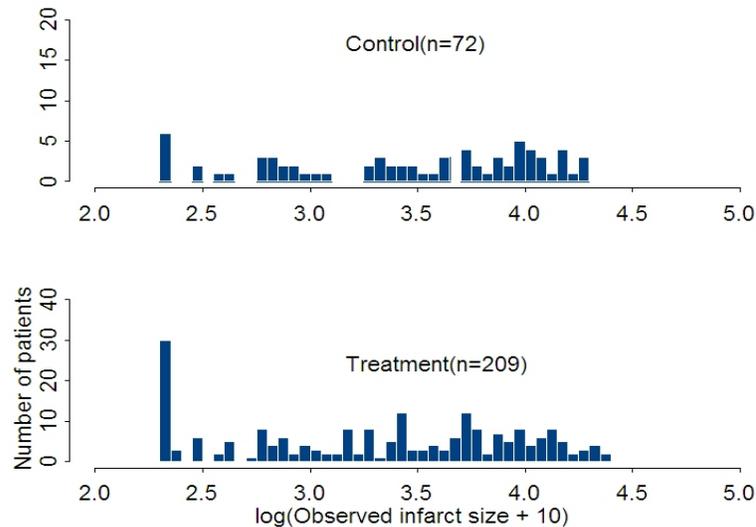


Figure 5. Distribution of log-transformed infarct size in Control and AO therapy groups.

To address concerns about the impact of non-normality on the validity of the results, FDA requested that the sponsor conduct additional analysis using an alternative Bayesian model. The sponsor then re-analyzed the data using an ordinal logistic regression model (**Model OL**; see Appendix III for details) with five categories of infarct size: 0%, 1-7%, 8-21%, 22-39%, >39%. The ordinal logistic regression model resulted in a Bayesian posterior probability of superiority = 99.0%.

FDA also expressed a concern that the pre-specified hierarchical model on mean infarct size within each arm (Model M1) may not be a satisfactory way of borrowing from

AMIHOT I study to estimate the AMIHOT II treatment effect. FDA then suggested formulating a Bayesian hierarchical model in terms of treatment effect (i.e., difference in mean infarct size between the treatment and control groups) instead of parameters within each treatment arm. The sponsor re-analyzed the data using the new Bayesian hierarchical model (**Model H1**; see Appendix III for details). This model resulted in a Bayesian posterior probability of superiority = 97.7%.

The pre-specified Bayesian hierarchical model (Model M1) did not consider the structure of the four subgroups as combinations of two factors, time to reperfusion (<6 hours, 6-24 hours) and infarct location (Anterior MI, Non-Anterior MI). FDA suggested that rather than ignoring the structure and giving the four subgroups a random effect distribution, the sponsor should model the data such that the two factors and their interaction can be given separate random effects distributions. The sponsor then re-analyzed the data using the new Bayesian hierarchical model (**Model H2**; see Appendix III for details). This model resulted in a Bayesian posterior probability of superiority = 97.3%.

As described earlier, in the Descriptive Analysis section, for the AMIHOT II study the treatment effect varied by center and ranged from -27.9 to +9.0%. FDA expressed concern about how the center effect might impact the Bayesian analysis results. It was suggested to the sponsor to provide additional analysis with a random center effect term added to the Bayesian model. The sponsor then re-analyzed the data using the new Bayesian hierarchical model (**Model H3**; see Appendix III for details). This model resulted in a Bayesian posterior probability of superiority = 96.6%.

Given that the time to reperfusion has an effect on infarct size, FDA suggested the sponsor to provide additional analysis by including time to reperfusion as a continuous variable and treatment by time to reperfusion interaction effects into the new hierarchical model H1. This model resulted in a Bayesian posterior probability of superiority = 97.9%.

Further analysis was conducted without borrowing data from AMIHOT I trial for the effectiveness endpoint. The following tables display the results of models OL, M1, H1, H2 and H3 using informative (borrowing) and non-informative (non-borrowing) priors.

Table 15. Infarct size at 14 days – Bayesian Evaluation of Primary Effectiveness Endpoint using Ordinary Logistic Regression Model (Model OL), comparing Informative (Borrowing) and Non-Informative (Non-Borrowing) Priors

	Posterior Probability of Superiority
Informative Prior (Borrowing)	
Model OL	99.0%
Non-Informative Prior (Non-Borrowing)	
Model OL	95.4%

Table 16. Infarct size at 14 days – Bayesian Evaluation of Primary Effectiveness Endpoint, comparing Informative (Borrowing) and Non-Informative (Non-Borrowing) Prior Models M1, H1, H2 and H3

	Posterior Probability of Superiority
Informative Prior (Borrowing)	
Pre-specified Model (M1)	95.1%
New Hierarchical Model (H1)	97.7%
Two-way ANOVA Mean Structure Model (H2)	97.3%
Random Site effect (H3)	96.6%
Non-Informative Prior (Non-Borrowing)	
Pre-specified Model (M1)	94.0%
New Hierarchical Model (H1)	94.5%
Two-way ANOVA Mean Structure Model (H2)	94.5%
Random Site effect (H3)	89.3%

In summary, these additional analyses all produce high posterior probability that the mean infarct size in the treatment group is smaller than the mean infarct size in the control group.

6. POST-APPROVAL STUDY

The FDA review team, which includes an epidemiologist, has made the recommendation that if the TherOx Downstream AO System is approved, a post-approval study should be conducted as a condition of approval for this first-of-a-kind device. Throughout our review of the PMA, FDA and the sponsor have worked closely to design this potential study. A summary of the proposed Post-Approval Study (PAS) plan is provided as Appendix I of this summary.

APPENDIX I – Summary of Proposed Post-Approval Study

Proposed Post-approval Study

Note: The inclusion of a Post-Approval Study section in this summary should not be interpreted to mean that FDA has made a decision or is making a recommendation on the approvability of this PMA device. The presence of a post-approval study plan or commitment does not in any way alter the requirements for pre-market approval. A recommendation for approval from the Panel must be based on the pre-market data. The issues noted below are FDA's comments regarding a potential post-approval study should the panel find the device approvable following its discussions and deliberations of the pre-market data, and should the panel recommend a post-approval study.

The sponsor proposes to conduct the following post-approval study (referred to as the "SSO2 Therapy Post-Approval Study, January 2, 2009):

Study Design

The sponsor proposes to conduct a prospective, open label, multi-center, single arm study to evaluate SSO2 Therapy safety during commercial use in real world settings in patients following successful PCI/stenting within 6 hours after experiencing acute anterior myocardial infarction. Results will be compared to the clinical outcomes in a similar AMI patient population from the HORIZONS study.

The main objectives are:

1. To evaluate clinical outcomes in a cohort of real world patients receiving SSO2 Therapy during commercial use by interventional cardiologists
2. To evaluate major complications, patient outcomes with adjunctive pharmacologic use.
3. To evaluate clinical device and procedural success during commercial use.

Study Hypotheses

The Null or alternative hypothesis is formulated as follows:

Null Hypothesis H_0 : $\Pi_1 - \Pi_0 \geq \Delta$

Alternative Hypothesis: $\Pi_1 - \Pi_0 < \Delta$

where Π_1 represents the occurrence rate of the MACE as established in the HORIZONS study and Δ is the largest acceptable difference between the study rate and the established rate. The sponsor chooses Δ to be 6%.

Patient Population and Sample Size

Qualifying anterior STEMI patients treated with PCI /Stenting within 6 hours of symptoms onset who receive SSO2 Therapy as an adjunct to their index procedure.

Key Inclusion Criteria:

The patient agrees to participate in this study by signing the Institutional Review Board-approved Informed Consent form. Qualifying patients will have anterior AMI with successful PCI and stenting less than six hours after time of symptom onset.

Key Exclusion Criteria:

Inability to obtain Informed Consent, cardiogenic shock and intra-aortic balloon pump (IABP) patients and patients with significant co-morbidities that may compromise the primary endpoint evaluation at one year.

404 patients will be enrolled consecutively in this study at 20-40 sites across the United States. Data from all study sites will be pooled for analysis.

Study Endpoints

Primary Endpoint: Composite incidence rate of Major Adverse Cardiac Events (MACE) defined as death, myocardial infarction (MI) and target vessel revascularization at 1 year.

Secondary Endpoint: Death (any cause) assessed at 1 year (and evaluated by an exact 95% exact confidence interval with a desired upper bound of less than 6.5%).

Additional Safety Data

- Individual MACE component event rates assessed at 30 days, 180 days and at 1 year
- Stent occlusion events assessed at 30, 180 days and at 1 year
- Bleeding events classified as serious through 30 days (or date of discharge from index procedure)
- Clinical, device, and technical success

Follow-Up Visits and Length of Follow-Up

Clinical follow-up will occur at 30, 180 days and at 1 year. Investigator or designee may conduct follow-up as telephone contact or office visit.

Enrollment Plan and Follow-Up Measures

The point of enrollment occurs when a patient or patient's legally authorized representative has provided written informed consent and only TherOx SSO2 Therapy is

initiated immediately post index PCI / Stent procedure. The study will sequentially enroll all consenting patients who have met these criteria.

Data collection

An independent clinical events committee (CEC) will review and adjudicate according to pre-specified definitions for each of the clinical data elements, including: death, MI, stroke, target vessel revascularization, and SAE bleeding.

Statistical Analysis

The analysis of the primary outcome variable, the 1-year MACE rate, will be based on the large-sample (Gaussian approximation or z) non-inferiority test of two proportions comparing the control data from the HORIZONS study with the results from the AO Therapy group obtained from the current investigation.

The mortality rate at one year will be evaluated using an exact 95% confidence interval based on the method of Clopper and Pearson.

Stent occlusion event rates at 30 days, 180 days and 1 year will be evaluated through proportions and the use of 95% exact confidence intervals. A similar analysis will be conducted for bleeding events classified as serious. For descriptive purposes, the results for both the SSO2 Therapy and HORIZONS data groups will be reported in parallel.

Appendix II – What is Bayesian Statistics?

Bayesian statistics is an approach for learning from evidence as it accumulates. The Bayesian approach uses Bayes' Theorem to combine prior information with current information on a quantity of interest. The Bayesian idea is to consider the prior information and the trial results as part of a continual data stream, in which inferences are being updated each time new data become available.

When good prior information on clinical use of a device exists, the Bayesian approach may enable this information to be incorporated into the statistical analysis of a trial.

The prior distribution

As an illustration, suppose that the Greek letter θ represents a parameter in a clinical trial. The initial knowledge about θ prior to data collection is represented by the prior distribution for θ , which we denote in symbols as $P(\theta)$. Suppose θ is the rate of a serious adverse event. Its possible values lie between 0 and 1. The prior distribution might give preference to lower values of θ (see Figure 1). The probability that θ takes on any particular set of values is determined by the area under the curve for those values. So the prior probability that the adverse event rate θ is greater than 0.4 (the shaded area) is about 0.38.

An *informative* prior distribution gives preferences to some values of the quantity of interest as being more likely than others (See Figure 1). Lack of preference among the values or lack of information can be represented through a *non-informative* prior distribution (e.g., a uniform prior which indicates no preference for any value of θ).

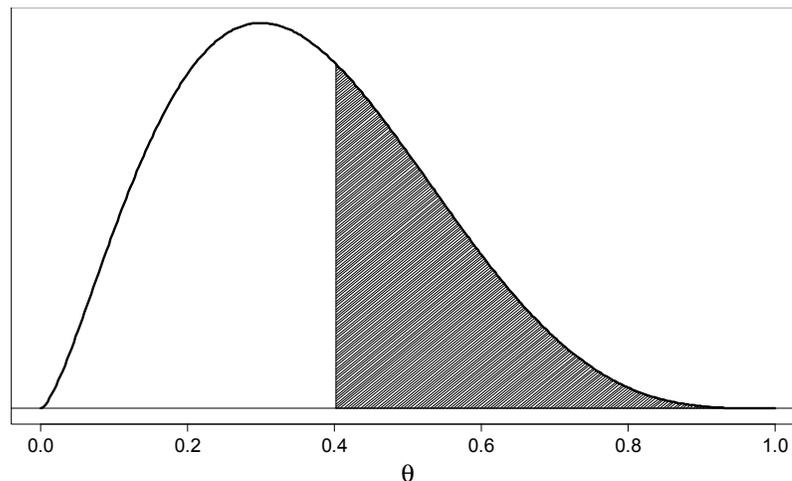


Figure 1. Example of a unimodal, right-skewed prior distribution for a serious adverse event rate, denoted by θ . The prior probability that θ is greater than 0.4 (the shaded area) is about 0.38.

The likelihood of the observed data

Now suppose outcomes have been obtained from a clinical trial. The likelihood function is a mathematical representation of the relationships between observed outcomes and the parameter θ . The likelihood function can be expressed in symbols by $P(\text{data} | \theta)$, which is

the conditional probability of observing the data given a specific value of the parameter θ , for each possible value of θ .

The posterior distribution

The final objective is to obtain the posterior distribution, the probabilities of the possible values of the parameter θ conditional on the observed data, which can be denoted in symbols as $P(\theta | \text{data})$. Bayes' theorem is used to update the prior distribution for θ , $P(\theta)$, via the likelihood, $P(\text{data} | \theta)$, to obtain the posterior distribution for θ , $P(\theta | \text{data})$. At the conclusion of the trial, the information about θ is summarized by this posterior distribution, and Bayesian inferences are based on it.

As an example, Figure 2 shows the posterior distribution that would be obtained if we started with the prior shown in Figure 1 and observed data with 1 adverse event in 10 patients. Since the adverse event rate observed in these patients is 0.10, the distribution has shifted further to the left (that is, it now favors even lower values for θ). The posterior probability that θ is greater than 0.4 (the shaded area) is about 0.04. The probability that the adverse event rate is greater than 0.4 has been reduced from about 0.38 (the prior probability) to about 0.04 (the posterior probability) by the favorable trial results.

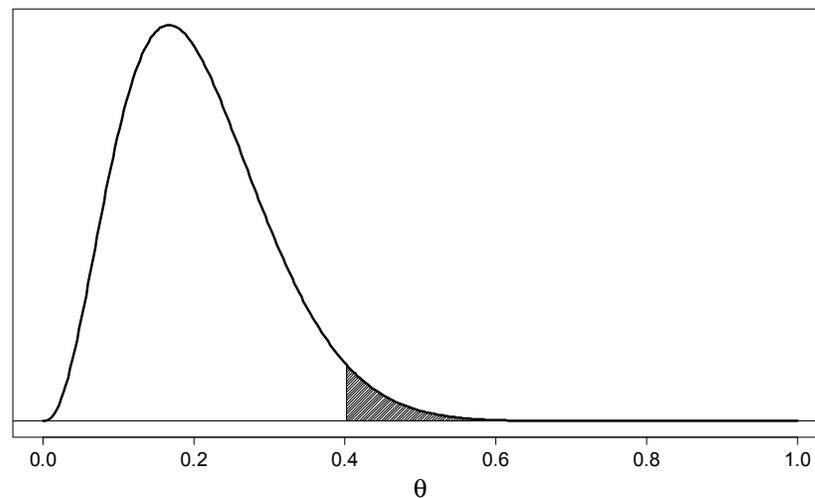


Figure 2. Example of a unimodal, right-skewed posterior distribution for a serious adverse event rate, denoted by θ , after observing one adverse event in 10 patients and updating the prior probability in Figure 1. The posterior probability that θ is greater than 0.4 (the shaded area) is about 0.04.

The posterior distribution that has been obtained today may serve as a prior distribution when more data are gathered. The more information that is accrued, the less uncertainty there may be about the posterior distribution for θ . If enough data are collected, the relative importance of the prior distribution will be negligible compared to the likelihood.

Bayesian inferences are based on the posterior distribution. For example, a Bayesian decision procedure might rule out a set of parameter values if the posterior probability of the parameter values (given the observed data) is small.

A pre-specified decision rule is used to demonstrate hypotheses that define safety and effectiveness with reasonable assurance. For Bayesian trials, one common type of decision rule considers that a hypothesis has been demonstrated (with reasonable assurance) if its posterior probability is large enough (e.g., 95 or 99 percent).

Exchangeability

Exchangeability is a fundamental concept underlying statistical inference. It can be of particular importance in Bayesian trials. Formally, we would say that units (patients or trials) are considered *exchangeable* if the probability of observing any particular set of observations on those units is invariant to any re-ordering of the units.

Exchangeability of patients

In a clinical trial, patients within the trial are usually assumed to be exchangeable. Under exchangeability, patient outcomes are not expected to depend on the order in which the patients were enrolled, the order in which the outcomes are observed, or any other re-indexing or re-numbering of the patients.

If patients in the trial are exchangeable with patients in the population from which they were sampled (e.g., the intended use population), then inferences can be made about the population on the basis of data observed on the trial patients. Thus, the concept of a *representative sample* can be expressed in terms of exchangeability.

Exchangeability of trials

For a Bayesian clinical trial, another level of exchangeability might be assumed. Namely, the trial can be assumed to be exchangeable with other previous trials when the previous trials are considered to be good prior information. The assumption of trial exchangeability enables the current trial to “borrow strength” from the previous trials, while acknowledging that the trials are not identical in all respects. Thus, exchangeability is important in the development of realistic models for combining trial data with prior information.

Bayesian Hierarchical Model

Bayesian hierarchical modeling is a specific methodology you may use to combine prior results with a current study to obtain estimates of safety and effectiveness parameters. The name hierarchical model derives from the hierarchical manner in which observations and parameters are structured. Some Bayesian analysts refer to this approach as “borrowing strength.” For device trials, the amount of strength borrowed can be translated into sample size, and the extent of borrowing depends on how closely results from the new study reflect the prior experience.

If results are very similar, the current study can borrow considerable strength. As current results vary from the previous information, the current study borrows less and less. Very different results borrow no strength at all, or even potentially “borrow negatively”. In a regulatory setting, hierarchical models can be very appealing: They reward having good prior information on device performance by lessening the burden in demonstrating safety and effectiveness. At the same time, the approach can protect against over-reliance on previous studies that turn out to be overly optimistic for the pivotal study parameter.

An example of a hierarchical model

Suppose you want to combine information on the success probabilities from two earlier studies of an approved device with results from a new study. You may decide to use two levels in a hierarchical model: the patient level and the study level.

The first (patient) level of the hierarchy assumes that within each study (current or historical), patients are exchangeable. Patients from previous studies are not, however, exchangeable with patients in the current study, so patient data from the earlier studies and the current study may not be simply pooled.

The second (study) level of the hierarchy applies a model that assumes the success probabilities from the previous studies and the current study are exchangeable, but the success probabilities may differ. This assumption is prudent since you are not sure if patients from the prior experience (i.e., the previous studies) are directly exchangeable with the patients from the current study. However, the success probabilities from all three studies are related in that they are assumed exchangeable. As a result, the previous studies provide some information about the success probability in the current study, although not as much information as if the patients in the three groups were directly poolable.

Analyzing a Bayesian Clinical Trial

The results, conclusions, and interpretation of a Bayesian analysis all rely on the posterior distribution. Consequently, results and conclusions for a Bayesian trial are based only on the posterior distribution.

Hypothesis testing

For Bayesian hypothesis testing, one can use the posterior distribution to calculate the probability that a particular hypothesis is true, given the observed data.

Interval estimation

Bayesian interval estimates are based on the posterior distribution and are called *credible intervals*. If the posterior probability that an endpoint lies in an interval is 0.95, then this interval is called a 95 percent *credible interval*.

APPENDIX III – Statistical Models

1. Model M1

For the Primary Effectiveness Endpoint (Infarct Size) Evaluation:

The mean values for study $i = 1, 2$ (1=AMIHOT I, 2=AMIHOT II) and subgroup j ($j = 1, 2, 3, 4$ for study $i = 1$ and $j = 1$ for study $i = 2$) are parameterized as:

$$\begin{aligned}\mu_{ij}^C &= \text{Mean for Control group} = \mu_0 + \omega_j^C + \gamma_i^C \\ \mu_{ij}^T &= \text{Mean for AO Therapy group} = \mu_{ij}^C + \delta_0 + \omega_j^T + \gamma_i^T,\end{aligned}$$

where μ_0 is the grand mean for the control group, δ_0 describes the overall treatment versus control difference, ω_j^C represents the subgroup effect and γ_i^C describes the study effect in the control arm, and ω_j^T represents the subgroup effect and γ_i^T describes the study effect in the treatment minus control differences.

Since the infarct size (say y) ranges from 0 to 1, the transformed response, $\log(y+10)$, is constrained to lie between 2.3 and 4.7 roughly. For the primary effectiveness endpoint evaluation, the model was specified as:

$$\begin{aligned}\log(y_{ijk}^C + 10) &\sim \text{Normal}(\mu_{ij}^C, \sigma_C^2) \\ \log(y_{ijk}^T + 10) &\sim \text{Normal}(\mu_{ij}^T, \sigma_T^2) \\ \mu_{ij}^C &= \mu_0 + \omega_j^C + \gamma_i^C \\ \mu_{ij}^T &= \mu_{ij}^C + \delta_0 + \omega_j^T + \gamma_i^T, \\ \omega_j^C &\sim \text{Normal}(0, \phi_\omega^2); \gamma_i^C \sim \text{Normal}(0, \phi_\gamma^2) \\ \omega_j^T &\sim \text{Normal}(0, \tau_\omega^2); \gamma_i^T \sim \text{Normal}(0, \tau_\gamma^2) \\ \phi_\omega &\sim \text{Uniform}(0.01, 0.67); \phi_\gamma \sim \text{Uniform}(0.01, 0.10) \\ \tau_\omega &\sim \text{Uniform}(0.01, 0.67); \tau_\gamma \sim \text{Uniform}(0.01, 0.10) \\ \sigma_C &\sim \text{Uniform}(0.01, 2.0); \sigma_T \sim \text{Uniform}(0.01, 2.0) \\ \mu_0 &\sim \text{Normal}(3.2, 0.7^2); \delta_0 \sim \text{Normal}(0, 0.7^2)\end{aligned}\tag{Model M1}$$

where y_{ijk}^C denotes the infarct size of the k th Control subject in study i subgroup j (k runs from 1 to n_{ij}^C), and, similarly, y_{ijk}^T denotes the infarct size of the k th AO Therapy subject in study i subgroup j (k runs from 1 to n_{ij}^T). The rationale for the chosen hyper-priors in the model is as following

- (i) $\mu_0 \sim \text{Normal}(3.2, 0.7^2)$. The grand mean for control infarct size is centered around a prior mean that corresponds to 15 on the original scale. The standard deviation of 0.7 then gives a 99.7% prior probability that the grand mean can be between 0 and 100.
- (ii) $\delta_0 \sim \text{Normal}(0, 0.7^2)$. The overall mean for the treatment minus control difference can be anywhere from 0 to 100 on the original scale.
- (iii) $\omega_j^C \sim \text{Normal}(0, \phi_\omega^2); \gamma_i^C \sim \text{Normal}(0, \phi_\gamma^2); \phi_\omega \sim \text{Uniform}(0.01, 0.67); \phi_\gamma \sim \text{Uniform}(0.01, 0.10)$. This is a vague prior for the subgroup effects in the control

group (which can easily span the full range of the data). Study random effects for the control group have a standard deviation no larger than 0.10 on the transformed scale. This suggests that if the mean in a particular control subgroup is 15 on the original scale, then study-specific means for that subgroup could possibly vary from 8 to 23. The stronger prior on study effects is used to combat the problem of having only two study effects for which we are attempting to estimate a variance component.

(iv) $\phi_i^T \sim \text{Normal}(0, \tau_\omega^2)$; $\gamma_i^T \sim \text{Normal}(0, \tau_\gamma^2)$; $\tau_\omega \sim \text{Uniform}(0.01, 0.67)$; $\tau_\gamma \sim \text{Uniform}(0.01, 0.10)$. The same comments noted above for the control random effects standard deviations, except that in the treatment case, the parameters refer to differences between the treatment and control means.

(v) $\sigma_C \sim \text{Uniform}(0.01, 2.0)$; $\sigma_T \sim \text{Uniform}(0.01, 2.0)$. The control and treatment group standard deviations for individual measurements should be very precisely determined by the data, and thus we specify only that these values are certain to be less than 2.0 on the transformed scale.

Inference will be based on the posterior distribution of the treatment minus control mean difference in study 2, subgroup 1, i.e. $(\mu_{21}^T - \mu_{21}^C) = \delta_0 + \omega_{21}^T + \gamma_{21}^T$, given the AMIHOT II and the AMIHOT I data. If the posterior probability is greater than 95%, the device will be claimed effective in term of the primary effectiveness endpoint. Based on this success criterion, the following is a table of simulated average study success rate for three different scenarios.

$\mu_{21}^T - \mu_{21}^C$		Study success rate (In term of the primary effectiveness endpoint)
On log (y +10) scale	On original y scale	
0.00	0.00	5.0%
-0.20	-5.0	85.4%
-0.25	-6.5	96.0%

2. Model OL

Ordinal logistic regression model with categories corresponding to cutoff of infarct size: 0%, 1-7%, 8-21%, 22-39%, >39% is specified as follows:

$$\begin{aligned}
 X_{ijtk} &\sim \text{Multinomial}(1, \pi_{ijt}) \\
 \pi_{ijt,w} &= q_{ijt,w-1} - q_{ijt,w}, w=1, \dots, 5 \\
 \text{logit}(q_{ijt,w}) &= -(\kappa_w + \mu_{ijt}), w=1, \dots, 4 \\
 q_{ijt,0} &\equiv 1, q_{ijt,5} \equiv 0 \\
 \mu_{ijt} &\equiv \gamma_i + \delta_j + \omega_t + \beta_{it} + \alpha_{jt} \\
 \omega_2 &\sim N(0, 10^2); \omega_1 \equiv 0 \\
 \gamma_i &\sim N(0, \phi_\gamma^2); \delta_j \sim N(0, \phi_\delta^2) \\
 \beta_{it} &\sim N(0, \phi_\beta^2); \alpha_{jt} \sim N(0, \phi_\alpha^2)
 \end{aligned}$$

$$\begin{aligned}
\varphi_{\gamma} &\sim U(0.01, 0.67); \varphi_{\delta} \sim U(0.01, 0.67); \\
\varphi_{\beta} &\sim U(0.01, 0.10); \varphi_{\alpha} \sim U(0.01, 0.67) \\
\kappa_1 &\sim N(0, 10^6) \mathbf{1}_{(-\infty, \kappa_2)}; \kappa_2 \sim N(0, 10^6) \mathbf{1}_{(\kappa_1, \kappa_3)} \\
\kappa_3 &\sim N(0, 10^6) \mathbf{1}_{(\kappa_2, \kappa_4)}; \kappa_4 \sim N(0, 10^6) \mathbf{1}_{(\kappa_3, \infty)}
\end{aligned}
\tag{Model OL}$$

where π_{ijt} is a 5-tuple of probabilities corresponding to the 5 possible outcome bins for a subject in study i , subgroup j , and treatment arm t ; the 5 components of $\pi_{ijt} = (\pi_{ijt,1}, \dots, \pi_{ijt,5})$ are specified as differences in the cumulative complementary probabilities ($q_{ijt,0}=1, q_{ijt,1}, \dots, q_{ijt,5}=0$); the log-odds for $-q_{ijt,w}$ for $w=1, \dots, 4$ are assumed to be equal to a cut point κ_w plus the mean μ_{ijt} , the components of the mean and their distributions are modeled as in the normal hierarchical model (see Model H1 for more detail), and the cutpoints are assumed to have vague normal distributions but are restricted to be in the order $\kappa_1 < \kappa_2 < \dots < \kappa_4$. Superiority is adjudicated by the posterior probability computation

$$P(\omega_2 + \alpha_{12} - \alpha_{11} + \beta_{22} - \beta_{21} > 0 \mid \text{data from AH1, AH2}),$$

(*i.e.*, superiority means that treatment arm 2 is more likely to have lower values of the ordinal outcome) and the main summary measure is the odds ratio $\varphi \equiv \exp(\omega_2 + \alpha_{12} - \alpha_{11} + \beta_{22} - \beta_{21})$.

The ordinal logistic regression model assumes proportional odds, *i.e.* that μ_{ijt} describes the common log-odds increment between each successive outcome category.

3. 3. Model H1

The mean values for study $i = 1, 2$, subgroup j ($j = 1, 2, 3, 4$ in study $i = 1$ and $j = 1$ only for study $i = 2$), treatment arm $t = 1$ (Control), 2 (AO Therapy) are parameterized as:

$$\mu_{ijt} = \mu_0 + \gamma_i + \delta_j + \omega_t + \beta_{it} + \alpha_{jt}$$

where μ_0 (grand mean) and ω_2 (average AO effect) are “fixed” effects (direct vague Normal prior distributions), ω_1 is set to zero for identifiability, and the terms γ_i (study effects), δ_j (subgroup effects), β_{it} (study by treatment arm effects) and α_{jt} (subgroup by treatment arm effects) are random effects drawn from Normal distributions with mean zero and standard deviations that are parameters in the model. For this model, the hypothesis of superiority is evaluated by the posterior probability $P(\omega_2 + \alpha_{12} - \alpha_{11} + \beta_{22} - \beta_{21} < 0 \mid y)$.

We note that this model has two “fixed” effects, $2+4+4+8 = 18$ random effects, 4 random effects standard deviations, and two data standard deviations. It is similar to our prespecified model, but has 6 additional random effects terms. This model specification should allow for more flexibility in the model, and may lead to higher degrees of borrowing from AMIHOT I where this is warranted. The complete model is written as

$$y_{ijkt} \sim N(\mu_{ijt}, \sigma_t^2)$$

$$\begin{aligned}
\mu_{ijt} &= \mu_0 + \gamma_i + \delta_j + \omega_t + \beta_{it} + \alpha_{jt} \\
\mu_0 &\sim N(0, 10^2) \\
\omega_2 &\sim N(0, 10^2); \omega_1 \equiv 0 \\
\gamma_i &\sim N(0, \varphi_\gamma^2); \delta_j \sim N(0, \varphi_\delta^2) \\
\beta_{it} &\sim N(0, \varphi_\beta^2); \alpha_{jt} \sim N(0, \varphi_\alpha^2) \\
\varphi_\gamma &\sim U(0.01, 0.67); \varphi_\delta \sim U(0.01, 0.67); \\
\varphi_\beta &\sim U(0.01, 0.10); \varphi_\alpha \sim U(0.01, 0.67) \\
\sigma_1 &\sim U(0.01, 2.0); \sigma_2 \sim U(0.01, 2.0)
\end{aligned}$$

(Model H1)

4. Model H2

We adjust model H1 to incorporate the two-way ANOVA mean model for the subgroup effect. We replace the index j for subgroup by two indices for reperfusion time ($r = 1$ for less than 6 hours and $r=2$ for greater than 6 hours) and location ($l=1$ for Anterior, $l=2$ for Non-Anterior). The resultant model H2 is defined as:

$$\begin{aligned}
y_{irlkt} &\sim N(\mu_{irlt}, \sigma^2) \\
\mu_{irlt} &= \mu_0 + \gamma_i + \zeta_r + \psi_l + \xi_{rl} + \omega_t + \beta_{it} + \eta_{rlt} \\
\mu_0 &\sim N(0, 10^2) \\
\omega_2 &\sim N(0, 10^2); \omega_1 \equiv 0 \\
\gamma_i &\sim N(0, \varphi_\gamma^2); \zeta_r \sim N(0, \varphi_\zeta^2) \\
\psi_l &\sim N(0, \varphi_\psi^2); \xi_{rl} \sim N(0, \varphi_\xi^2) \\
\beta_{it} &\sim N(0, \varphi_\beta^2); \eta_{rlt} \sim N(0, \varphi_\eta^2) \\
\varphi_\gamma &\sim U(0.01, 0.67); \varphi_\zeta \sim U(0.01, 0.67); \\
\varphi_\psi &\sim U(0.01, 0.67); \varphi_\xi \sim U(0.01, 0.67); \\
\varphi_\beta &\sim U(0.01, 0.10); \varphi_\eta \sim U(0.01, 0.67) \\
\sigma_1 &\sim U(0.01, 2.0); \sigma_2 \sim U(0.01, 2.0)
\end{aligned}$$

(Model H2)

5. Model H3

We adjust model H1 to incorporate random site (indexed by s) and site-by-treatment effects. The resultant model H3 is defined as:

$$\begin{aligned}
y_{ijkt} &\sim N(\mu_{ijt}, \sigma^2) \\
\mu_{ijt} &= \mu_0 + \gamma_i + \delta_j + \omega_t + \beta_{it} + \alpha_{jt} + \varphi_s + \theta_{st} \\
\mu_0 &\sim N(0, 10^2) \\
\omega_2 &\sim N(0, 10^2); \omega_1 \equiv 0 \\
\gamma_i &\sim N(0, \varphi_\gamma^2); \delta_j \sim N(0, \varphi_\delta^2) \\
\beta_{it} &\sim N(0, \varphi_\beta^2); \alpha_{jt} \sim N(0, \varphi_\alpha^2) \\
\varphi_\gamma &\sim U(0.01, 0.67); \varphi_\delta \sim U(0.01, 0.67); \\
\varphi_\beta &\sim U(0.01, 0.10); \varphi_\alpha \sim U(0.01, 0.67) \\
\varphi_\varphi &\sim U(0.01, 0.67); \varphi_\theta \sim U(0.01, 0.67) \\
\sigma_1 &\sim U(0.01, 2.0); \sigma_2 \sim U(0.01, 2.0)
\end{aligned}$$

(Model H3)

6. Safety Model

The Bayesian hierarchical model for the primary safety endpoint evaluation was specified as:

$$\begin{aligned}r_{ij}^C &\sim \text{Binomial}(n_{ij}^C, \pi_{ij}^C) \\r_{ij}^T &\sim \text{Binomial}(n_{ij}^T, \pi_{ij}^T) \\ \text{logit}(\pi_{ij}^C) &= \lambda_{ij}^C \\ \lambda_{ij}^C &= \mu_0 + \omega_j^C + \gamma_i^C \\ \pi_{ij}^T &= \pi_{ij}^C + \delta_0 + \omega_j^T + \gamma_i^T \text{ (truncated to } [0, 1]) \\ \omega_j^C &\sim \text{Normal}(0, \phi_\omega^2); \gamma_i^C \sim \text{Normal}(0, \phi_\gamma^2) \\ \omega_j^T &\sim \text{Normal}(0, \tau_\omega^2); \gamma_i^T \sim \text{Normal}(0, \tau_\gamma^2) \\ \phi_\omega &\sim \text{Uniform}(0.01, 0.30); \phi_\gamma \sim \text{Uniform}(0.01, 0.30) \\ \tau_\omega &\sim \text{Uniform}(0.001, 0.10); \tau_\gamma \sim \text{Uniform}(0.001, 0.033) \\ \mu_0 &\sim \text{Normal}(-2.6, 0.52); \delta_0 \sim \text{Normal}(0, 0.22)\end{aligned}$$

where r_{ij}^C denotes the number of patients in the control group with a MACE in study i (i runs from 1 to 2, 1=AMIHOT I, 2=AMIHOT II) subgroup j (j runs from 1 to 4), and, similarly, r_{ij}^T denotes the number of patients in the treatment group with an MACE in study i subgroup j . μ_0 is the grand mean of MACE rates for the control group (on logit scale), δ_0 is the overall treatment versus control difference in MACE rates (i.e. on risk difference scale), ω_j^C represents the subgroup effect and γ_i^C describes the study effect in the control arm (these parameters are both on the logit scale), and ω_j^T represents the subgroup effect and γ_i^T describes the study effect in the treatment effects (these parameters are both on the risk difference scale). For the rationale for the chosen hyper-priors, please see the appendix at end of this review.

Inference will be based on the posterior distribution of the treatment minus control difference in MACE rate in study 2, subgroup 1, i.e. $(\pi_{21}^T - \pi_{21}^C) = \delta_0 + \omega_1^T + \gamma_2^T$, given the AMIHOT II and the AMIHOT I data.