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1. PURPOSE

   The COOL-AMI EU Pivotal Trial Statistical Analysis Plan is a document that defines the analysis of the data of EDC-3135 COOL-AMI EU Pivotal clinical trial conducted in Europe by ZOLL Circulation, Inc., in accordance with ICH regulations and under Good Clinical Practices in accordance with ISO 14155.

2. SCOPE

   The COOL-AMI EU Pivotal Trial Statistical Analysis Plan defines the detailed specifications for the analysis of the clinical trial data.

3. REFERENCE

   None

4. REQUIREMENTS

   4.1 Clinical trial data shall remain confidential per HIPAA and applicable European Regulations.

   4.2 Clinical trial data will be maintained in the Clinical Affairs files.

5. APPENDICES

   5.1 Appendix A – Statistical Analysis Plan ……..……26 pages

6. REVISION HISTORY

Rev.	Description	Originator	Effective Date
1	Document was initially released in CT system # CT01-030 AMI EU Pivotal Trial – Statistical Analyses Plan on 16 June 2017	Lori Houghtaling	10/01/2018
2	Revised header and format to comply with ZeDS formatting. Edited to account for suspension of trial	Shikha Gautam	See signature page

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APPENDIX A

STATISTICAL ANALYSIS PLAN

FOR

COOL-AMI EU PIVOTAL TRIAL: A MULTICENTER, PROSPECTIVE, RANDOMIZED-CONTROLLED TRIAL TO ASSESS THE SAFETY AND EFFECTIVENESS OF COOLING AS AN ADJUNCTIVE THERAPY TO PERCUTANEOUS INTERVENTION IN PATIENTS WITH ACUTE MYOCARDIAL INFARCTION (PROTOCOL NO: EDC-3135)

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Statistical Analysis Plan

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1 Abbreviations and Definitions

AE	Adverse event
AMI	Acute myocardial infarction
BMI	Body mass index
CD	Cardiac death
CI-TVR	Clinically-indicated target vessel revascularization
cMR	Cardiac magnetic resonance
CRF	Case report form
DMC	Data Monitoring Committee
IRI	Ischemia reperfusion injury
IS	Infarct size
ITT	Intent-to-Treat
IVTM	Proteus™ intravascular temperature management system
KCCQ	Kansas City cardiomyopathy questionnaire
MACE	Major adverse cardiac event
MI	Myocardial infarction
n	Number
PCI	Percutaneous coronary intervention
PP	Per-protocol
SAP	Statistical analysis plan
TH	Therapeutic hypothermia
TVR	Target vessel revascularization

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2 Introduction

The Statistical Analysis Plan provides prospective, detailed specification for the analyses for **Cool-AMI EU Pivotal Trial: A Multicenter, Prospective, Randomized-Controlled Trial To Assess The Safety And Effectiveness Of Cooling As An Adjunctive Therapy To Percutaneous Intervention In Patients With Acute Myocardial Infarction (EDC 3135).** The background and objectives of the document is a reiteration of the study protocol supplemented with additional details as appropriate. This document will support protocol and associated amendments updated throughout the life of the study. It was finalized upon completion of study closeout before database lock.

2.1 Background

Coronary heart disease complicated by acute myocardial infarction (AMI) remains a leading cause of death and disability worldwide. AMI most commonly occurs when a coronary artery becomes occluded by thrombus following the rupture of an atherosclerotic plaque. Factors that may affect the size of the subsequent infarction include duration of ischemia, size of ischemic territory, collateral blood flow, and myocardial metabolic rate. Long-term sequelae of AMI include ventricular remodeling, loss of ventricular function, congestive heart failure, dysrhythmias, and sudden death.

Although major gains have been made in improving the outcome of patients suffering AMI, and early myocardial reperfusion with the use of thrombolytic therapy or primary percutaneous coronary intervention (PCI) are effective, morbidity and mortality remain substantial. This may be because restoration of blood flow to the ischemic myocardium can itself induce injury through myocardial "ischemia reperfusion injury" (IRI), which can be defined as that portion of the ischemia-reperfusion

continuum which is preventable by treatment initiated after restoration of blood flow[1]. It has been proposed that 50% of the final infarct size may be a function of IRI[1].

Ischemia reperfusion injury is protean in its components, likely including free radical and reactive oxygen species, disordered vasculature, inflammatory injury, programmed cell death, and pathologic remodelling among others[2]. Unfortunately, the cascading nature of these events challenge and, in the end, may defeat the single molecular target pharmacologic model. The long list of failed IRI pharmacologic agents includes antioxidants, calcium channel blockers, anti-inflammatory drugs, sodium hydrogen exchange inhibitors, among others, has led some to question the importance of reperfusion injury in the myocardium[3].

Therapeutic hypothermia (TH) has been studied for many years as a potential therapy for ischemia and reperfusion[4,5,6,7,8,9,10]. The past few years have seen development of a broad literature reporting both laboratory and clinical trials of mild post-reperfusion TH in the treatment of disease entities as diverse as acute cardiac arrest, stroke, and myocardial infarction, among others. Unlike single pharmacologic agents, TH has the potential to modify and ameliorate multiple pathways of injury.

2.2 Purpose of the analyses

The objective of this randomized clinical trial is to evaluate the safety and effectiveness of therapeutic hypothermia, using the ZOLL Proteus IVTM System, as an adjunctive therapy for patients presenting with acute anterior myocardial infarction and undergoing PCI, in comparison with patients with acute anterior myocardial infarction and undergoing PCI only.

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3 Study Objectives and Endpoints

3.1 Study Objectives

This is a confirmatory trial to evaluate safety and effectiveness of therapeutic hypothermia using ZOLL Proteus IVTM System for patients with acute anterior MI in comparison with anterior MI patients who only undergo PCI. Efficacy is established by demonstrating a relative reduction of 20% in mean anterior myocardial infarct size (IS), as determined by Cardiac Magnetic Resonance (cMR) imaging at 4-6 days post infarct in the Test Arm (cooling + PCI) compared to the Control Arm (PCI only). Infarction Size (IS) is defined as % Left Ventricular Mass as measured by Cardiac Magnetic Resonance (cMR) imaging.

Infarct Size (IS) will be assessed by Cardiac Magnetic Resonance (cMR) at 4 – 6 days following the index procedure and is a measurement of “myocardial reperfusion injury” by a Core Lab.

The trial is considered to have met the primary efficacy endpoint if the Test Arm demonstrates a 20% relative reduction in mean infarct size (defined as a 3.5% absolute reduction) compared to the Control Arm.

Furthermore, safety will be evaluated throughout the trial on basis of non-inferiority, with 6% established as the margin of non-inferiority.

3.2 Endpoints

Primary Effectiveness Endpoint:

Mean anterior myocardial infarct size (IS), as determined by Cardiac Magnetic Resonance (cMR) imaging at 4-6 days post infarct in the Test Arm (cooling + PCI) compared to the Control Arm (PCI only). Infarction Size (IS) is defined as % Left Ventricular Mass as measured by Cardiac Magnetic Resonance (cMR) imaging. Infarct Size (IS) will be assessed by Cardiac Magnetic Resonance (cMR) at 4 – 6 days following the index procedure.

Primary Safety Endpoint:

Per-patient rate of composite Major Adverse Cardiac Events (MACE) subjects, defined as Cardiac Death (CD), All Myocardial Infarction (all MI) and Clinically-Indicated Target Vessel Revascularization (CI-TVR) at 30 days; non-inferiority to the control.

Additional Safety Endpoints:

The following clinical components of MACE will be evaluated for per-patient rate at 30 days:

- Death (Cardiac, Vascular, Non-Cardiovascular)
- Myocardial Infarction (MI)
  - Attributable to target vessel (TV-MI)
  - Not attributable to target vessel (NTV-MI)
- Target Vessel Revascularization (TVR)
  - Clinically-indicated TVR
  - Not clinically-indicated TVR
- All coronary revascularization
- Stent Thrombosis
  - Timing (Acute, Sub-acute)
  - Evidence (Definite and Probable)

3.3 Derived variables

All endpoints will be in case report form (CRF) except for MACE event, which will be derived according to the following:

MACE event is a composite variable considered as any of the following events: Cardiac Death (CD), All Myocardial Infarction (all MI) and Clinically-Indicated Target Vessel Revascularization (CI-TVR).

4 Study Methods

4.1 General Study Design and Plan

A multicenter, prospective, interventional, randomized-controlled trial. Randomization will be in a 1:1 ratio, Test Arm (PCI + Cooling) or Control Arm (PCI alone). This is an unblinded trial with randomization using stratified by site using permutated blocks.

Subjects will be screened and randomized according to the following flow diagram:

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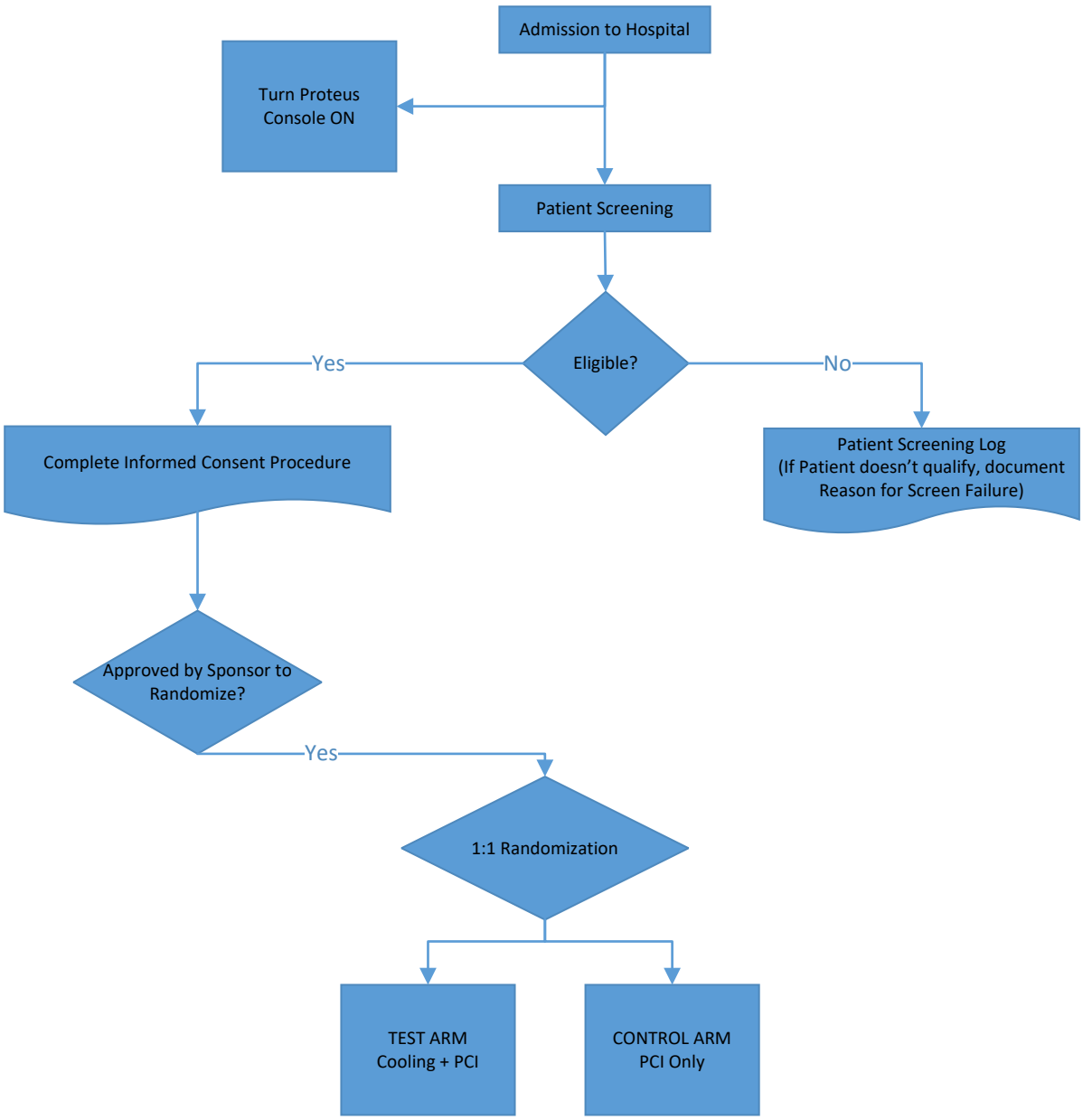

Figure 1 Screening and Enrolment Flow

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Follow-up after randomization (post-procedure, either Control with PCI only, or Test with PCI and Cooling) are described below:

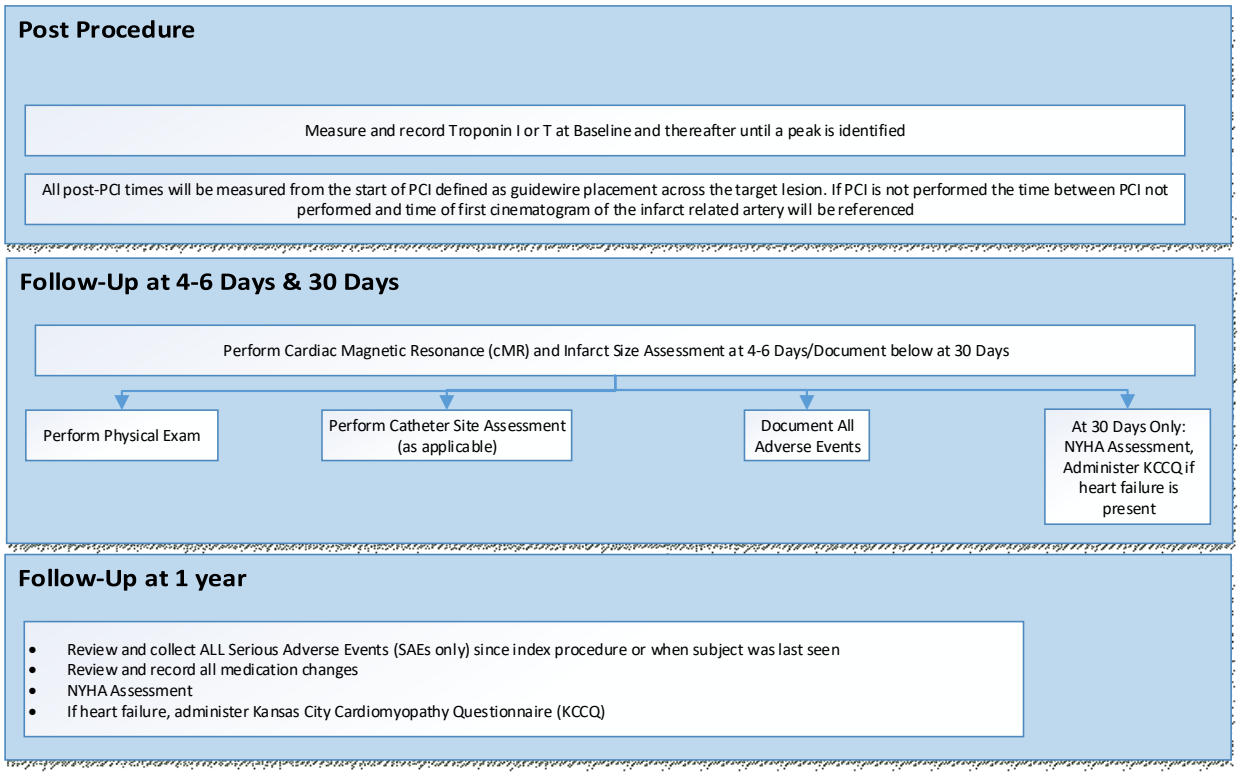

Figure 2 All Patient Procedures

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4.2 Inclusion-Exclusion Criteria and General Study Population

4.2.1 Inclusion Criteria:

All Inclusion Criteria must be answered YES for subject to satisfy Inclusion Criteria:

1. The patient is ≥ 18 years of age.
2. The patient must have symptoms consistent with AMI (i.e. chest pain, arm pain, etc.) and unresponsive to nitroglycerin, with symptoms beginning greater than 30 minutes but less than 6 hours prior to presentation at hospital.
3. Qualifying Infarct location:
   Roll-In subjects: Evidence of Acute Anterior or Inferior MI with ST- segment elevation of ≥ 0.2 mV in two or more anterior or inferior contiguous precordial leads (V1 –V4).
   Randomized subjects: Evidence of Acute Anterior MI only with ST-segment elevation of ≥ 0.2 mV in two or more anterior contiguous precordial leads.
4. The patient is eligible for PCI.
5. The patient is willing to provide written informed consent to participate in this clinical trial.

4.2.2 Exclusion Criteria:

All Exclusion Criteria must be answered NO for subject to satisfy Exclusion Criteria:

1. The patient has had a previous Myocardial Infarction.
2. The patient is experiencing cardiogenic shock (systolic blood pressure [SBP] <100 mmHg, HR>100 bpm and arterial oxygen saturation (pulse oximetry) ≤95% without additional oxygen
3. The patient is presenting with resuscitated cardiac arrest, atrial fibrillation, or Killip risk stratification class II through IV.

4. The patient has an aortic dissection or requires an immediate surgical or procedural intervention other than PCI.
5. The patient has known history of Congestive Heart Failure (CHF), hepatic failure, end-stage kidney disease or severe renal failure (clearance < 30ml/min/1.73m²).
6. The patient is febrile (temperature > 37.5 °C) or has experienced an infection with fever in the last 5 days.
7. The patient has a known previous CABG.
8. The patient has a known recent stroke within 90 days of admission.
9. Cardio-pulmonary decompensation that has occurred en route to the hospital or, in the opinion of the physician, that is imminent or likely to occur following presentation to the clinical site.
10. Contraindications to hypothermia, such as patients with known hematologic dyscrasias which affect thrombosis (e.g., cryoglobulinemia, sickle cell disease, serum cold agglutinins) or vasospastic disorders (such as Raynaud's or thromboangitis obliterans).The patient has a known hypersensitivity or contraindication to aspirin, heparin, or sensitivity to contrast media, which cannot be adequately pre-medicated.
11. Any contraindication to cardiac MRI, or any implant in the upper body which may cause artifacts on cardiac MRI imaging.
12. The patient has a known hypersensitivity or contraindication to aspirin, heparin, or sensitivity to contrast media, which cannot be adequately pre-medicated.
13. The patient has a known history of bleeding diathesis, coagulopathy, cryoglobulinemia, sickle cell anemia, or will refuse blood transfusions.
14. The patient has a height of <1.5 meters (4 feet 11 inches).
15. The patient has a known hypersensitivity or contraindication to buspirone hydrochloride or Pethidine (Meperidine) and/or has been treated with a monoamine oxidase inhibitor in the past 14 days.
16. Patient has a known history of severe hepatic or renal impairment, untreated hypothyroidism, Addison's disease, benign prostatic hypertrophy, or urethral stricture that in the opinion of the physician would be incompatible with Pethidine administration.
17. The patient has an Inferior Vena Cava filter in place (IVC).
18. The patient has a pre-MI life expectancy of <1 year due to underlying medical conditions or pre-existing co-morbidities.
19. The patient has a known, unresolved history of drug use or alcohol dependency, or lacks the ability to comprehend or follow instructions.
20. The patient is currently enrolled in another investigational drug or device trial.
21. The patient is apprehensive about or unwilling to undergo the required MRI imaging at follow-up, has a documented or suspected diagnosis of claustrophobia, or has Gadolinium allergy, or is in permanent Atrial Fibrillation.
22. The patient has received thrombolytic therapy en-route to the hospital.
23. The patient shows clinical evidence of spontaneous reperfusion as observed symptomatically and/ or from baseline ECG findings (partial or complete ST resolution in baseline ECG prior to informed consent and randomization).
24. The patient is a vulnerable subject, for instance, a person in detention (i.e., prisoner or ward of the state).
25. The patient is a female who is known to be pregnant.

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4.3 Randomisation and Blinding

Randomization will be applied using an internet based Interactive Web Response Systems (IWRS). In the trial, randomization will be done using random permuted blocks (based on procedure outlined in Pocock SJ. Clinical Trials: A Practical Approach. Wiley, Chichester, 1983), stratified by site, with 1:1 allocation ratio using a randomization list. At randomization, inclusion and exclusion criteria will be verified, and confirmation of informed consent signature will be done.

While investigator and subject will not be blinded to treatment group, all cMR analyses that provide value for the endpoint will be performed by a core laboratory which will be blinded to all clinical data including treatment group.

4.4 Study Variables

Observations and records of important variables will be assessed according to the following schedule along with acceptable time-windows. Measurements outside scheduled assessment times will be considered protocol deviations.

Notable evaluations include the following:

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For Control subjects:

Procedure/ Interval	Baseline / Enrollment	Immediately prior to reperfusion (PCI)Post-PCI	Catheter Removal	Discharge*	Follow-Up @ 4-6 Days	Follow-Up @ 30 Days (±7 days)	Follow-Up @ 12 months (±14 days)	Unscheduled Visit
Trial Eligibility & Informed Consent	**upon arrival to hospital**							
Physical Exam and Medical History	**X**			**X**				
Catheter Insertion Time	**X**							
Catheter Removal Time			**X**					
Temperature Documented	**X**							
Vital Signs	**X**							
Blood Studies RBC's, WBC's, Hct, Hgb, Platelets, Neutrophils, Eosinophils	**X**							
Pro BNP							X	
Lab Studies BUN, Creatinine, Na, K, Ca, Mg, Cl, P, lactic acid, glucose, amylase, lipase	**X**							
Any Medication Use	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Troponin I or T	**Collect at Baseline**	**Collected only if peak reached**	**Collected only if peak reached**					
12 lead ECG	**X**							
Adverse Events		**X**	**X**	**X**	**X**	**X**	**X**	**X**
Cardiac Magnetic Resonance (cMR)					**X**			
NYHA Assessment							**X**	**X**
KCCQ Assessment							**X**	**X**

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For Test subjects:

Procedure/ Interval	Baseline / Enrollment	Initiation of Cooling	Immediately prior to reperfusion (PCI)	Maintenance of Target Temp 32 ±1°C	Rewarming to 36°C	Catheter Removal	Discharge	Follow-Up @ 4-6 Days	Follow-Up @ 30 Days (±7 days)	Follow-Up @ 12 months (±14 days)	Unscheduled Visit
Trial Eligibility & Informed Consent	**upon arrival to hospital**										
Physical Exam and Medical History	**X**						**X**				
Anti-Shivering Protocol	**X**			**X**[c]							
Cold Saline Infusion		**X**									
Catheter Insertion Time		**X**									
Catheter Removal Time						**X**					
Temperature Documented	**X**	**X**	**X**	**every 30 min during 3 hr cooling**							
Temperature Data Download						**X**					
Vital Signs	**X**	**X**	**X**	**every 30 min**							
Blood Studies RBC's, WBC's, Hct, Hgb, Platelets, Neutrophils, Eosinophils	**X**			**upon reaching target temperature**	**upon reaching normothermia**						
Pro BNP										**X**	
Lab Studies BUN, Creatinine, Na, K, Ca, Mg, Cl, P, lactic acid, glucose, amylase, lipase	**X**										
Any Medication Use	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Troponin I or T	**X**	**Collected only if peak reached**	**Collected only if peak reached**	**Collected only if peak reached**	**upon reaching normothermia, Collected only if peak reached**	**Collected only if Peak reached**					
12 lead ECG	**X**										
Adverse Events		**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Catheter Access Site Assessment						**X**	**X**	**X**			
Cardiac Magnetic Resonance (cMR) imaging								**X**			
NYHA Assessment										**X**	**X**
KCCQ Assessment										**X**	**X**

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5 Sample Size

Sample size considerations are based on both the primary effectiveness analysis.

The primary effectiveness analyses is designed to detect a relative reduction of 20% in mean anterior myocardial infarct size (IS), as determined by Cardiac Magnetic Resonance (cMR) imaging at 4-6 days post infarct in the Test Arm (cooling + PCI) compared to the Control Arm (PCI only). The absolute magnitude of a relative reduction of 20% depends on the mean IS in the control arm, which is assumed to be approximately 17 %LV. Therefore, the treatment effect of interest is an absolute difference of 3.5 %LV. Therefore, the treatment effect of interest is an absolute difference of 3.5 %LV.

The null hypothesis is that the mean IS in the Test Arm is equal to the mean IS in the Control Arm. The assumed standard deviation is 12 %LV and the final analysis will be conducted using a two-sided test at the alpha=0.044 level of significance (adjusted for the two interim analyses). Based on these assumptions, the required total sample to detect a mean difference of 3.5 %LV with 80% power is 384 subjects (192 subjects per group). Allowing for a potential dropout rate of 24%, the planned total sample size is 500 subjects (250 subjects per group).

H_0: $\mu_T = \mu_C$
H_A: $\mu_T \neq \mu_C$

Null hypothesis:

The null hypothesis is that the mean IS in the Test Arm is equal to the mean IS in the Control Arm.

Alternative hypothesis:

The mean %LV in the control arm is not equal to mean of control arm.

This 20% relative reduction is defined as absolute value 3.5 %LV and accounted for in our sample size calculation as treatment effect. This assumption is based on previous studies with anterior infarct size measured with cMR reporting between 17-20% absolute %LV in anterior infarct (***Tables 1 & 2***). Therefore, a relative reduction of 20% can vary depending on the mean infarct size of the control arm. Assuming a representative mean infarct size of ~17% in controls, we assume absolute difference of 3.5 %LV is equivalent to 20% mean anterior infarct size would be an adequate detection limit for effect.

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Table 1: Clinical trials reporting anterior mean infarct size measured by cMR 4-6 days in PCI trials (Control Group Only) and calculated 20% relative reduction

Study name	Anterior n	Mean infarct size	Standard Deviation	20% relative reduction
APEX-AMI[37]	**60**	**16.6**	**10.7**	**3.3**
LIPSIAABCIXIMAB[38]	**63**	**25.3**	**16.1**	**5.1**
LIPSIA-STEMI[39]	**38**	**18**	**16.0**	**3.6**
CRISP-AMI [40]*	**142**	**37.5**	**20.1**	**7.5**
INFUSE-AMI[41]	**172**	**17.3**	**10.2**	**3.5**
RAPID-MI ICE[1]	**7**	**19.7**	**8.5**	**3.9**
CHILL-MI[33]	**21**	**26.5**	**10.9**	**5.3**
AMI EU PILOT	**21**	**23.3**	**12.0**	**4**

*>60% are large proximal infarcts

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Table 2: Hypothermia trials using cMR measured infarct size as primary outcome

	RAPID-MI ICE (2009)	CHILL-MI (2013)	AMI EU Pilot (2017)	Pooled AMI EU Pilot, RAPID-MI-ICE, CHILL-MI
n (Control vs Cooled)	7 vs 5	21 vs 15	21 vs 19	49 vs 39
Control Mean LV%	19.7	26.5	23.3	24.5
20% reduction in infarct	3.94	5.3	4.7	4.9
Std Dev (control)	8.5	10.9	12.0	10.5
Std Dev (cooled)	6.5	9.3	10.3	11.0

The potential impact of variations in control infarct size and variability is presented in ***Table 3***.

Table 3: Sample size estimates with alternative standard deviation and detection limit

Mean Difference in infarct size for detection (%)	Standard Deviation	Estimated Sample Size	Total Enrolment (with 20% drop-out)
3.0	9	288	360
3.0	10	355	444
3.0	11	430	534
3.0	12	506	636
3.5	9	212	264
3.5	10	260	330
3.5	11	314	396
3.5	12	374	468
4.0	9	162	204
4.0	10	200	252
4.0	11	240	300
4.0	12	286	360

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The safety endpoint is a composite endpoint. In consideration regarding power of this study, expected incidence is based on a literature review of acute MI hypothermia trials that combined six studies: Dixon et al, COOL MI, ICE-IT, RAPID MI-ICE, CHILL-MI, VELOCITY[11] which resulted in a 30-day MACE rate of 6.6% in the Control patients and 7.5% in treatment patients. Previously, AMIHOT II trial defined 30-day MACE rate comprised of death, reinfarction, target vessel revascularization, and stroke used a non-inferiority hypothesis with a 6% equivalence delta and 7% in the Control patients[12].

The hypothesis for the primary safety endpoint is the following:

$\mathbf{H_0}: \pi_T \geq \pi_C + 6\%$

$\mathbf{H_A}: \pi_T < \pi_C + 6\%$

π_T and π_C are the underlying proportion of patients having a MACE event.

An enrolment of 500 would be able to demonstrate 91% power and 95% 1-sided significance with alpha=0.05. The safety endpoint will be considered to have been met if there is a high posterior probability of non-inferiority [i.e. P ($\pi t < \pi c + 6\% > 95\%$)]. With 20% dropout, the power becomes 86%.

6 General Considerations

6.1 Timing of Analyses

The final analysis will be performed after enrolment is considered complete and all cMR and follow-ups have been performed except for patients lost to follow-up—for lost-to-follow up patients, reason will be documented. For final analyses, data will be cleaned in compliance with Data Management Plan and the finalization and approval of SAP documents.

6.2 Analysis Populations

The Intention-to-Treat (ITT) analysis set will be used for primary efficacy statistical analyses and summaries. The ITT population includes subjects who have signed an informed consent and have been randomized to the Test Arm or the Control Arm of the trial. ITT subjects will be evaluated according to the group to which they were randomized.

The Per-Protocol (PP) analysis set will also be evaluated. The PP population includes those subjects who met all inclusion and exclusion criteria, were randomized to either the Test or Control arm, received the treatment to which they were randomized, and complied substantially with the treatment timeline and steps of this protocol without major protocol violations.

The Safety Analysis Set, which includes all ITT subjects, will be used to evaluate safety endpoints. For the safety analysis, subjects will be followed for all adverse events for 12 months post procedure. Additionally, all subjects in this set will be confirmed as followed for 12 months for the incidence of Adverse Events, Serious Adverse Events (SAEs), Death and Heart Failure (as assessed by NYHA and Kansas City Cardiomyopathy Questionnaire (KCCQ), as applicable).

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6.3 Covariates and Subgroups

Subgroups to be evaluated for heterogeneity of infarct size using an interaction model with treatment variable and the following subgroup variable: age (<65 vs >65 years), BMI (<25 vs >=25), BMI (<30 vs >=30), sex, door to balloon time (<60 minutes, 60-90 minutes, >90 minutes), ischemic time (≤4 hours vs >4 hours), post-TIMI flow (0-2 vs 3), temperature at PCI (<32°C, 32-35°C, >35°C). Wald test or t-test p-value will be reported for each group as appropriate depending on final linear regression model.

In order to evaluate clinical characteristics in association with infarct size, separate univariate models may be considered for exploratory analysis: ischemic time, country and/or center. Analysis of covariance models will be used. Evaluation for independence, normality, homoscedasticity, and linearity will be applied. Square root transformation will be used if assumption is violated. Beta coefficient, standard error, 95%CI, and p-values will be reported. From among the variables with individually significant associations, after selection of single covariates from among any collections of highly collinear covariates based on their univariate associations with infarct size, a multivariate model will be built using forward and backward stepwise variable selection, to determine the variables with independently significant associations with risk, using a criterion of $p \leq 0.05$.

6.4 Missing Data

Missing data will be quantified per variable (%), with missing data patterns noted through summarization by centre and compared by treatment group.

For primary effectiveness analysis, missing values will not be imputed given that the trial never reached complete enrolment.

6.5 Data Monitoring

6.5.1 Practical Measures to Minimise Bias

Clinical monitoring will be conducted according to Good Clinical Practise and Clinical Monitoring Plan. Furthermore, the Data Management Plan describes study specific processes for data review and handling, describing the strategy to review data for omissions, inaccuracies and inconsistencies. Adverse event review and handling (SOP5-016 Rev 4 Clinical Trial Adverse Event Review And Handling) defines the process to protect safety of subjects and ensure the integrity of the safety data.

The results of unblinded interim analyses – both efficacy and safety -- will be available only to members of the DMC for decision making. Reports will also be provided for government authorities with oversight regarding conduct of clinical trials upon request. No information will be publicly available following interim analyses except for decision whether the trial is continued or discontinued.

6.5.2 Documentation of Interim Analyses

Documentation of interim analyses will be made according to Control Review and Approval of Clinical Trial Documents (SOP5-017). Data snapshot, programming, and reports will be preserved for the trial archive.

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6.6 Multi-centre Studies

This is a multicentre study intended to be analysed as whole. Differences between sites are designed to be minimized by using it as a stratification factor. Individual centre results will be combined. Given that enrolment per centres may be small and there will be up to 70 centres, no adjustment for centres will be made for primary efficacy analyses. Treatment-by-centre interactions will only be tested as an exploratory analysis if a single centre contributes >10% of the patients in total analyses population. In this particular case, treatment will be considered as a fixed effect and the centre as a random effect.

6.7 Multiple Testing

For this trial, there is only one primary effectiveness outcome with two interim analyses. Overall significance value is preserved for interim analyses with established stopping rules preserving the overall type 1 error rate of alpha for <0.05.

For primary and secondary safety analyses, given the number of statistical tests, adjustment for multiplicity is considered counterproductive for considerations of safety as there is no control of the type I error for a single hypothesis. Tests will be conducted using one-sided test at alpha 0.05 level of significance.

All other analyses will be conducted using two-sided tests at the alpha=0.05 level of significance.

7 Summary of Study Data

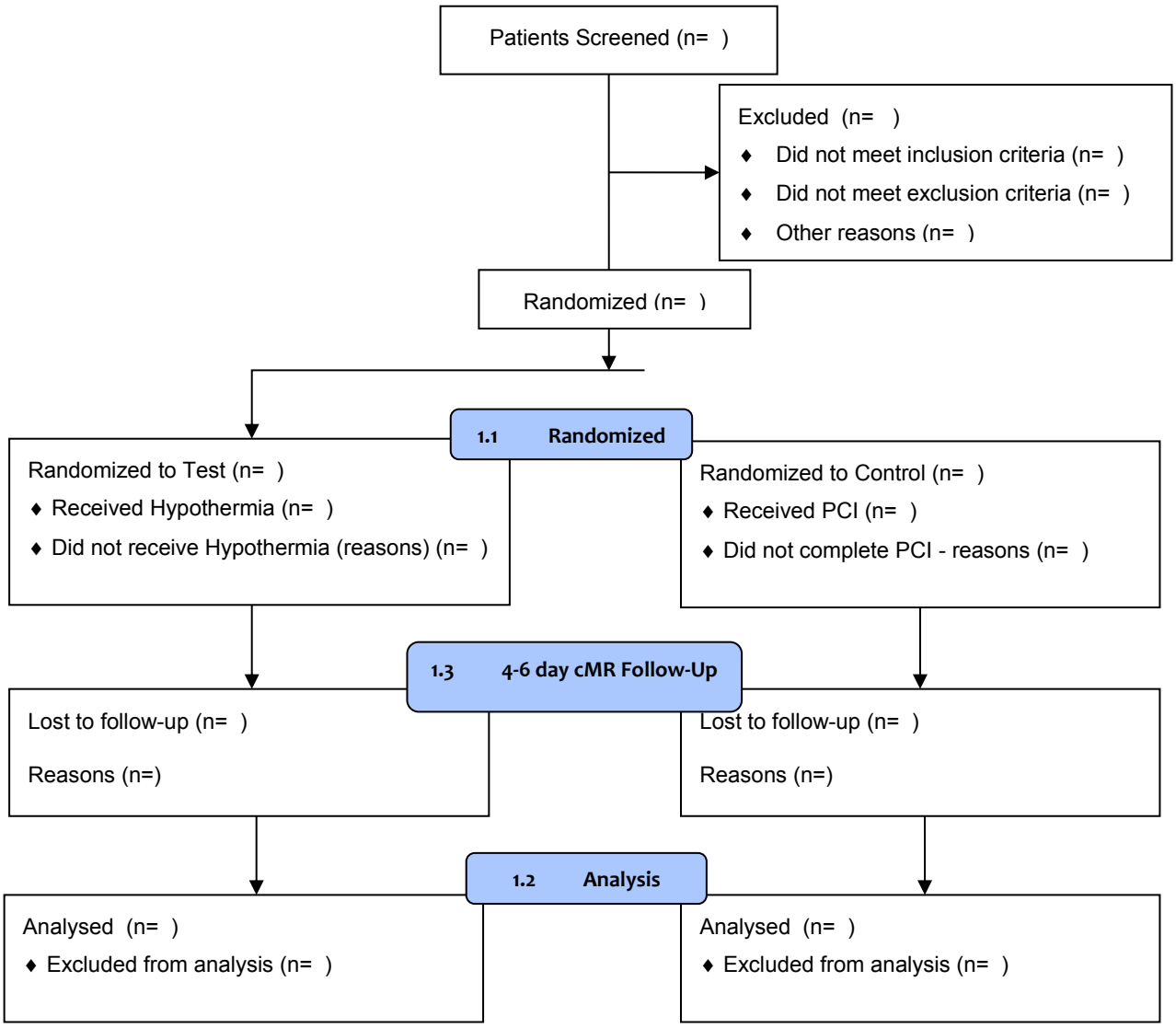
Data will be sorted by treatment and centre and structured with columns for Test and Control. Descriptive and efficacy figures and tables will be produced for ITT and PP population. All

continuous variables will be summarised using the following descriptive statistics: n (non-missing sample size), mean, standard deviation, median, maximum and minimum. The frequency and percentages (based on the non-missing sample size) of observed levels will be reported for all categorical measures. In general, all tables will be annotated with population size relevant to the table/treatment, including any missing observations.

7.1 Subject Disposition

Number screened and randomized will be recorded and tabulated in *Study Eligibility* CRF according to variable for eligible (yes/no) and reason for no enrolment. *Enrollment & Randomization* CRF will document randomization assignation in variable "Assigned Treatment Group" that will determine the number of patients in each treatment arm. Patients reached 4-6 day cMR follow-up, patients reaching 30 day follow-up, patients with 12 months follow-up, and patients reaching completion of study will be tabulated according to documentation for date and time of visit according to follow-up CRFs: *4-6 Day Follow-Up, 30 Day Follow-Up,* and *12 Month Follow-Up.* Study exits and Lost to follow-up will be recorded on *Study Exit* CRF in free text field. Death will be recorded in the *Adverse Events* form.

An example of a skeleton CONSORT diagram is provided below for evaluation of efficacy:



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7.2 Protocol Deviations

Major protocol deviations or violation include the following:

Subjects with deviations relating to eligibility will be considered in the ITT analyses set, but not the PP analyses set.

Subjects with the following deviations relating to protocol implementation will also be excluded in the PP analyses set but included in the ITT analyses set:

- No cMR follow-up at 4-6 days leading to no IS data available. Missing data will be treated according Section 6.
- cMR completed out of 10 day window leading to available of IS data.
- Repeat infarction prior to 4-6 day cMR

The summary statistics will be produced in accordance with section 6.

7.3 Demographic and Baseline Variables

Demographics and Baseline clinical characteristics: age, sex, height (cm), weight (kg), BMI, systolic blood pressure (mmHg), diastolic blood pressure (mmHg), heart rate (beats/min), respiration (breaths/min), tympanic temperature at baseline (degree Celcius), glucose (mmol/L), calcium (mmol/L), magnesium (mmol/L), creatinine (umol/L), alcohol usage(current/past), smoking history (current/past), and medical history: history of cardiovascular conditions, diabetes, hypertension, and dislipidemia.

Treatment parameters: door to randomization, door to balloon time, door to wire-crossing time, randomization to wire crossing, randomization to balloon, and total ischemic time.

The summary statistics will be produced in accordance with section 6.

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7.4 Medical History and Co-morbidities

Cardiac and non-cardiac medical history and comorbidities will be recorded in *Medical History* portion of CRF with reference to time of condition.

In particular: presence of diabetes, hypertension, dislipidemia, and previously known multivessel coronary disease will be summarized.

7.5 Prior and Concurrent Medications

Concurrent medications will be recorded in *Anti-Shivering Medications* and *Medication & Fluid* CRF. Summary statistics will be produced in terms of usage or total dosage for antishivering management including buspirone and pethidine. Usage of DAPT medications administered prior to procedure will be reported. These medications include heparin, aspirin, prasugrel, ticagrelor, clopidogrel, bivalirudin, and glycoprotein IIB/IIIa.

7.6 Treatment Compliance

Assessment of treatment compliance including submission of 4-6 day cMR for both Control and Test patients and availability of IS for analyses. For Test patients, compliance is additionally assessed as number of patients who are Cooled, assessed through the *Initiation of Cooling* CRF, which notes date and time of cooling initiation and the variable indicating “Initiation of Cooling – Not Done”. Other

measurements of compliance include the adherence to DAPT protocol, which is recorded in the Medications CRF.

The summary statistics will be produced in accordance with section 6.

Substantial protocol compliance for inclusion into Per-Protocol population is defined as the following:

- Received assigned treatment
    - Test subjects with no interrupted or problematic cooling
- cMR completed with available IS data within window (10 days)
- No repeat infarction prior to 4-6 day cMR

8 Efficacy Analyses

Efficacy variable IS (LV%) will be listed by subject within study centre. Data will be summarised by treatment group. N, Mean, Standard Deviation, Minimum and Maximum will summarise continuous efficacy variables. Plan in handling missing data for missing IS are documented in Section 6.

All assumptions for regression models will be assessed by viewing plots of the residual values. Transformation will be applied as appropriate as necessary for exploratory analysis adjusted by covariates including ischemic time.

8.1 Primary Efficacy Analysis

To evaluate anterior infarct size (%LV) in Control and Treatment Arm, summary statistics will be used; n, mean, standard deviation median, interquartile range, minimum, maximum will be reported. T-test (2-sided) or Wilcoxon rank-sum test (2-sided) will be used as appropriate to calculate p-value after evaluation for normality.

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9 Safety Analyses

To summarize incidence of adverse events, summary for all site reported events will be conducted on patient basis on the safety analysis set. Specifically, each patient will be counted once for an event and any repetitions will be ignored; the denominator will be the sample population size. Summaries will be produced by treatment (Test vs. Control) as well as an “All Patients” column. 1-sided Chi-square test or Fisher’s-exact test will be used as appropriate depending on whether number of patients are fewer than 5, in which case Fisher’s exact test will be used.

Only deviations from the aforementioned analytical and summary approaches will be noted in the subsequent subsections of section 9.

The only summarized variable is MACE, which is also a composite endpoint.

9.1 Adverse Events

The summary statistics will be produced in accordance with section 7. When calculating the incidence of adverse events, or any sub-classification thereof by treatment each subject will only be counted once and any repetitions of adverse events will be ignored; the denominator will be the total

population size. Incidence of specific AEs will be presented in summary form up to 30 days. For 12 months follow up, all AEs incidences will be summarized.

9.2 Deaths, Serious Adverse Events and other Significant Adverse Events

The summary statistics will be produced in accordance with section 7.

9.3 Clinical Laboratory Evaluations

A Core Lab is employed to ensure that difference between study centres are minimized for measurement of IS, which is the primary endpoint. For blood chemistry at baseline, while summary statistics including mean, median, standard deviation, and range will be presented, the CRF will also note whether the value is clinically significant or not to ensure that normal ranges have been provided by all centres and that outliers are noted.

9.4 Other Safety Measures

Vital signs are taken at baseline and reviewed and queried as appropriate regarding whether values are reasonable and compatible with life. DSMB will convene periodically to review safety data summaries.

10 Other Analyses

KCCQ, , and NT-proBNP at 12 months patients will be presented in summary form only for mean, median, standard deviation, interquartile range, and range. No formal statistical analyses will be conducted.

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11 Reporting Conventions

P-values ≥0.001 will be reported to 3 decimal places; p-values less than 0.001 will be reported as "<0.001". The mean, standard deviation, and quantiles will be reported to the same precision for decimal place as the original data.

12 Technical Details

Statistical analyses will be conducted using SAS and R and other statistical software as appropriate. Citations will be provided for all statistical software used.

Verification and validation of the primary efficacy and safety analyses will be provided by independent programming and analyses by a second analyst, who will also be provided an overview of the entire analyses. The second analyst will also verify code and results selected at random.

13 Listings of Tables, Listings and Figures

Listing of Tables

Table Title	Population	Endpoint	Time Point	Covariates or Subgroups	Summary Statistics
Randomization and Follow-ups	ITT	Subject disposition through the trial	Baseline, 4-6 day, 30 days, 12 months	Randomization	x (p%)
Protocol Deviations	ITT	Protocol deviations reported	Baseline, 4-6 day, 30 days, 12 months	Randomization	x
Baseline demographic and clinical characteristics	ITT	Demographics and clinical baseline variables	Baseline	Randomization	n, mean, SD, median, IQR, min, max, x (p%), p-value
Medical History	ITT	Subject medical history	Baseline	Randomization	x (p%), p-value
Treatment Description	ITT	Treatment variables	Baseline	Randomization	n, mean, SD, median, IQR, min, max, p-values
Baseline ECG and Angiographic Findings	ITT	Angiographic and Baseline ECG variables	Baseline	Randomization	x (p%), p-value
Cooling Procedure	ITT	Anti-shivering management, shivering, temperature at baseline, temperature at initiation of cooling, temperature at wire-crossing, duration of cooling phases, catheter indwell time, total volume of cold saline	Baseline	Randomization	n, mean, SD, median, IQR, min, max, x (p%), p-value
cMR Results	ITT and PP	cMR findings	4-6 day	Randomization and Treatment	n, mean, SD, median, IQR, min, max, p-value
Association of infarct size with covariates	ITT and PP	Association with covariates including age, BMI, sex, pre-TIMI flow, post-TIMI flow, DTB, Ischemic time, and temperature at PCI	4-6 day	NA	p-value
NYHA classification at 12 months	ITT	NYHA Classification	12 months	Treatment	x (p%), p-value
KCCQ summary at 12 months	ITT	KCCQ overall summary score and KCCQ clinical summary score	12 months	Treatment	n, mean, SD, median, min, max, p-value

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NT-proBNP summary at 12 months	ITT	NT-proBNP	12 months	Treatment	n, mean, SD, median, IQR, min, max, p-value
Clinical outcome summary (death, MI re-infarction, or TVR at 30 days)	Safety analysis set	MACE (Primary Safety)	30-days	Randomization	x (p%), p-value
Clinical components of mace summary	Safety analysis set	Additional Safety Endpoints	30 days	Randomization	x (p%), p-value
Subjects with serious adverse events summary within 30 days	Safety analysis set	All Serious Adverse Events	30 days	Randomization	x (p%), p-value
Subjects with non-serious adverse events summary within 30 days	Safety analysis set	All Non-Serious Adverse Events	30 days	Randomization	x (p%), p-value
Subjects with serious adverse events summary within 12 months	Safety analysis set	All Serious Adverse Events	12 months	Randomization	x (p%), p-value
Subjects with non-serious adverse events summary within 12 months	Safety analysis set	All Non-Serious Adverse Events	12 months	Randomization	x (p%), p-value
Subjects with serious adverse events of interest within 30 days	Safety analysis set	Serious adverse events of interest	30 days	Randomization	x (p%), p-value
Subjects with death and stent thrombosis within 12 months	Safety analysis set	Death and Stent Thrombosis	12 months	Randomization	x (p%), p-value
DAPT and Anti-Thrombotic Medication	ITT	DAPT and Anti-Thrombotic Medications used	Baseline	Randomization	x (p%), p-value

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Listing of Listings

Title	Population	Display Variables	Time Point	Sort Variable
Subjects not cooled	ITT	Randomization, Subject ID, Reason for not cooling	Baseline	Randomization
Protocol Deviations	ITT	Reasons for deviation	Baseline, 4-6 day, 30 days, 12 months	Randomization, Subject ID
Device Deficiency	ITT	Device type, device disposition, deficiency description	Baseline	Randomization, Subject ID
Serious Adverse Events	ITT	Adverse Event Number, Adverse Event, Adverse event start date, Outcome, Procedure relatedness, Device relatedness	Baseline, 4-6 day, 30 days, 12 months	Randomization, Subject ID, AE number
Non-Serious Adverse Events	ITT	Adverse Event Number, Adverse Event, adverse event start date, Outcome, Procedure relatedness, Device relatedness	Baseline, 4-6 day, 30 days, 12 months	Randomization, Subject ID, AE number
CEC adjudication results of MACE at 30 days	Safety analysis set	CEC adjudication of MACE	30 days	Subject ID, AE number

Listing of Figures

Title	Population	Type of graph	Horizontal Variables	Vertical Variables	Groupings	Statistics	Facets
CONSORT Diagram	ITT	Flow chart					NA
Temperature Over Time	ITT	Line	Time	Temperature	Randomization	Mean, SD	NA
Infarct Size	ITT and PP	Boxplot with Scatter	Treatment	Infarct Size (LV%)	Treatment	Mean, Median, IQR, absolute difference, relative difference, p-value	NA
Ejection Fraction	ITT and PP	Boxplot with Scatter	Treatment	Ejection Fraction (%)	Treatment	Mean, Median, IQR, absolute difference, relative difference, p-value	NA
Distribution of Ischemic time with infarct size	ITT and PP	Scatterplot	Ischemic time	Infarct size at 4-6 days	Treatment	NA	NA
Distribution of Ischemic time with infarct size	ITT and PP	Scatterplot	Ischemic time	Infarct size at 4-6 days	Treatment	N, 95% CI, beta coefficient, p-value, R^2, adjusted R^2	NA

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14 References

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