Official Title: **A prospective, double blind, randomized, placebo-controlled clinical trial of intracoronary infusion of immunoselected, bone marrow-derived Stro3 mesenchymal precursor cells (MPC) in the treatment of patients with STelevation myocardial infarction**

NCT Number: NCT01781390

Document Date: Protocol Version 10: 04 May 2017

The AMICI Trial

Allogeneic **M**esenchymal precursor cell **I**nfusion
In myo**C**ardial **I**nfarction

A prospective, double blind, randomized, placebo-controlled clinical trial of intracoronary infusion of immunoselected, bone marrow-derived Stro3 mesenchymal precursor cells (MPC) in the treatment of patients with ST-elevation myocardial infarction

Protocol Number ANG.AMI-IC001

Protocol Version: 10.0
(Applicable to all participating countries except The Netherlands and Sweden)

Protocol Date: 04 May 2017

Replaces: Protocol Version 9.0 (October 11, 2016)
EudraCT Number: 2010-020497-41

Sponsor: Mesoblast, Inc.
505 Fifth Ave., 3rd Floor
New York, NY10017
USA

Confidentiality Statement

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1.1 Study Administrative Structure

Protocol Title: *A prospective, double blind, randomized, placebo-controlled clinical trial of intracoronary infusion of immunoselected, bone marrow-derived Stro3 mesenchymal precursor cells (MPC) in the treatment of patients with ST-elevation myocardial infarction*

Protocol Number: ANG.AMI-IC001

Protocol Version: 10.0

Protocol Date: 04 May 2017

Short Title	**AMICI: A**llogeneic **M**esenchymal precursor cell **I**nfusion in myo**C**ardial **I**nfarction
Study Sponsor	**Mesoblast, Inc.** 505 Fifth Ave, 3rd floor New York , NY10017 USA Phone: 212-880-2060 Fax:212-880-2061
EU Legal Representative	**Mesoblast UK Limited** 5 New Street Square London, EC4A 3TW United Kingdom
Australian Sponsor	**Mesoblast Limited** Level 38, 55 Collins St. Melbourne, VIC 3000 Australia Phone: +61 3 9639 6036 Fax: +61 3 9639 6030
Sponsor's Responsible Medical Officer	[redacted]**, MD, MSc**
Sponsor's Contact	[redacted]**, MD, MSc**
Data Safety Monitoring Board [redacted]	[redacted]**, M.D.**

Coordinating Investigator	**, MD, FACC** United States of America Ph: Fax:
MPC Manufacturer and Supplier	USA Belgium
Contract Research Organization	USA Phone: Fax:
Central Clinical Laboratories	USA USA
Imaging Core Lab	USA Phone: Fax:

1.2 Sponsor Approval Page

Allogeneic **M**esenchymal precursor cell **I**nfusion
in myo**C**ardial **I**nfarction

A prospective, double blind, randomized, placebo-controlled clinical trial of intracoronary infusion of immuno-selected bone marrow-derived Stro3 mesenchymal precursor cells (MPC) in the treatment of patients with ST-elevation myocardial infarction

Protocol Number:	ANG.AMI-IC001
Protocol Version:	10.0
Protocol Date:	04 May 2017
EudraCT Number:	2010-020497-41
Sponsor:	Mesoblast, Inc. 505 Fifth Ave., 3rd Floor New York, NY 10017 USA

Mesoblast, Inc. Approval:

_____

[redacted] MD, MSc

[redacted]

1.3 Investigator Approval Page

Allogeneic **M**esenchymal precursor cell **I**nfusion
in myo**C**ardial **I**nfarction

A prospective, double blind, randomized, placebo-controlled clinical trial of intracoronary infusion of immuno-selected bone marrow-derived Stro3 mesenchymal precursor cells (MPC) in the treatment of patients with ST-elevation myocardial infarction

Protocol Number:	ANG.AMI-IC001
Protocol Version:	10.0
Protocol Date:	04 May 2017
Sponsor:	Mesoblast, Inc. 505 Fifth Ave., 3rd Floor New York, NY 10017 USA

Investigator's Name:

Address:

Telephone Number:

I, the Site Investigator named above, by signing below acknowledge the receipt of this protocol in its entirely and agree to conduct this study according to this protocol, Good Clinical Practices and all applicable code of federal regulations (CFRs) and guidelines.

_____	_____	_____
Investigator's Printed Name	**Signature**	**Date**

1.4 Contacts in Case of Emergency

Table 1: Emergency Contact Information

Role in Study	Name	Telephone Number and Email
Medical Director	[redacted], MD, MSc	Office: [redacted] [redacted]
Safety Officer	[redacted], MD	Office: [redacted] Mobile: [redacted] [redacted]

1.5 Study Synopsis

Protocol Title	A prospective, double blind, randomized, placebo-controlled clinical trial of intracoronary infusion of immunoselected, bone marrow-derived Stro3 mesenchymal precursor cells (MPC) in the treatment of patients with ST-elevation myocardial infarction
Sponsor	Mesoblast, Inc. 505 Fifth Ave., 3rd Floor New York, NY 10017 USA
Study Phase	2
Investigators and Clinical Sites	Approximately 25 clinical sites
Indication	*De novo* anterior wall myocardial infarction due to a lesion or occlusion of the left anterior descending (LAD) coronary artery.
Study Hypothesis	MPCs when administered intracoronary immediately after successful PCI with stenting in patients with first time acute anterior STEMI will result in amelioration of the early post-event inflammatory response and subsequent fibrotic scarring as well as promote the process of neo-angiogenesis in tissue where an ischemic condition exists or is developing. The net result will be: • decreased infarct size by short term protection of at-risk myocardium • increased long term salvage of myocardium resulting in decreased adverse left ventricular (LV) remodeling.
Objectives	**Primary Objective:** • To determine the safety and feasibility of intracoronary allogeneic, immuno-selected, bone marrow-derived Stro3 MPC delivery in the treatment of subjects with STEMI undergoing PCI of the LAD coronary artery. **Secondary Objectives:** • To explore a dose-response effect of intracoronary delivered MPC in the treatment of subjects with an anterior wall STEMI on LV remodelling, microvascular obstruction, and the relationship between time from onset of ischemic symptoms to primary PCI. • To determine the effect of intracoronary delivery of MPC on infarct size reduction in the treatment of subjects with STEMI undergoing primary PCI of the LAD coronary artery. • [redacted]

Study Design	This is a prospective, double-blind, randomized, placebo-controlled study that will enroll approximately 105 subjects with *de novo* anterior STEMI due to a lesion involving LAD coronary artery who undergo primary PCI at approximately 25 clinical study sites. This study will compare two doses of MPCs and a placebo control group. Study subjects will be randomly assigned in 1:1:1 fashion to receive either 12.5 Million or 25 Million MPCs or placebo (saline). Each group will have approximately 35 subjects. Potential subjects will be approached by a site investigator prior to PCI and must sign an informed consent form before initiation of the cardiac catheterization procedure in order to participate in this trial. Following successful and uneventful PCI and stenting of the culprit LAD lesion, the subjects will be randomized. The randomization and treatment assignment will be obtained from an interactive voice-response system (IVRS/interactive web response system (IWRS)). The following stratification for duration of cardiac ischemia will be performed to ensure balanced randomization across the treatment groups: • ≤2 hours • >2 hours to ≤6 hours • >6 to ≤12 hours. Eligible subjects will receive intracoronary delivery of the assigned treatment infused via a microcatheter into the stented culprit artery. The subjects randomized to MPCs will be infused at an infusion rate of 2 ml/min over approximately 60 minutes, including line flush [$2.5x10^5$ MPCs/min (12.5 M), $5.0x10^5$ MPCs/min (25 M)]. The subjects randomized to placebo will be infused placebo solution at 2 mL/min over approximately 60 minutes, including line flush (0 MPCs/min). The MPC product (12.5M and 25M MPCs) and the placebo solution will be diluted in 100mL 0.9% saline solution prior to infusion. The Sponsor will provide all sites with blinded treatment cryovials, which contain the different doses of MPCs or placebo solution. An intracoronary (IC) bolus of glyceryl trinitrate (GTN)/ nitroglycerin (NTG) (100-200 mcg) should be administered (blood pressure permitting) prior to the Thrombolysis in Myocardial Infarction (TIMI) flow assessment during the investigational agent infusion period as well as after completion of the investigational agent infusion and immediately prior to the final coronary

	angiographic imaging. After approximately 50% of the intracoronary infusion of investigational agent has been completed, an angiographic determination of coronary flow will be performed. The following guidelines will be used to determine if the remaining investigational agent should be infused: • The study infusion should be continued if either TIMI 2 or TIMI 3 flow is present in the absence of ALL of the following: o Sustained hypotension not responsive to fluid administration; o Clinical signs/symptoms indicating an acute cerebrovascular event; o Re-elevation of ST-segments if previously resolved with PCI; o Onset of the subject's symptoms of myocardial ischemia unresponsive to appropriate interventions; o Two episodes of sustained ventricular tachycardia (VT)/ventricular fibrillation (VF) requiring cardioversion (infusion can continue if a single episode of sustained VT/VF requiring cardioversion occurred). If for any reason, the site investigator withdraws a randomized subject prior to infusion of the investigational agent, the reason for early termination and data from the screening visit will be entered into the eCRF by the study site. The subject will not remain in the study. If for any reason, a subject's study infusion is halted due to safety considerations, the subject will remain in the study. A subject who prematurely withdraws from the study, post-study infusion, will remain in the study. Evaluation for safety will be performed for up to 24 months post infusion. Subjects will undergo cardiac magnetic resonance imaging (cMRI) and 2-D echocardiography (ECHO), Holter monitoring, clinical evaluation and laboratory testing. cMRI, ECHO monitoring will be performed at 2-7 days post infusion of study agent (MPCs or Placebo), as well as at Day 30 and at Month 6 after the procedure. Holter monitoring will be performed at 14 and 30 days, 3 and 6 months after the procedure. Clinical evaluation and laboratory testing will be performed at 6, 12, 18 and 24 hours post infusion of study agent (MPCs or Placebo), during the index hospitalization as well as at 14 and

	30 days and 3, 6, 12, 18 and 24 months after the procedure as outlined in Table 2 Schedule of Assessments and Procedures. An independent Data Safety Monitoring Board (DSMB) will review all relevant acute peri-procedural data, serious adverse events (SAE),other adverse events (AE), and efficacy data (if requested) periodically dependent on subject enrollment, and advise the Executive Steering Committee (ESC) regarding the progression of the study. The ESC will consist of the Coordinating Investigator, site investigators and representatives of and advisors to the Sponsor. A Clinical Events Committee (CEC) will review appropriate source documents and adjudicate (blinded per a priori procedure) all major adverse cardiovascular and cerebrovascular events (MACCE) defined as cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, or cardiac hospitalization due to heart failure. Target vessel (or other vessel) revascularization post index cardiac catheterization and new or worsening heart failure during the index hospitalization will be tracked as "Adverse Events of Special Interest" rather than MACCE. Subjects, Site personnel, Investigators will remain blinded until after all safety follow-up is completed. The DSMB may choose to be unblinded. The DSMB safety reviews to assess the frequency of total MACCE will be performed after the initial 15, 30, 60, and 90 subjects have been observed at Day 30 post the index cardiac catheterization. The final safety analysis will be performed at 24 months for all patients.
Population	Subjects age 18 and above who have been successfully treated within 12 hours of the onset of ischemic symptoms with standard care for a *de novo* STEMI (PCI and stent placement) involving the LAD coronary artery.
Efficacy Endpoints	**Primary Efficacy Endpoint:** • The primary efficacy endpoint is the change in LV end-systolic volume (LVESV) as assessed by cardiac MRI from baseline to 6 months post investigational agent infusion in each MPC treatment group compared with the Placebo group.

	Secondary Efficacy Endpoints: • The change in LVESV as assessed by 2D-echocardiography from baseline to 6 months post investigational agent infusion. • The change in relative infarct size as assessed by late contrast enhancement MRI (% infarct volume/total LV tissue volume) from baseline to 6 months post investigational agent infusion. • Additional functional efficacy endpoints will be assessed with the following diagnostic studies: o Cardiac MRI at 2-4 days, 30 days and at Month 6. o LVEF o LVESV o LVEDV o Left ventricular wall thickness and thickening in all segments including infarct area o Regional wall motion score o Myocardial microvascular obstruction measured as reduced signal intensity in the region of interest o MI size measured in the region of interest as late contrast enhancement o Myocardial salvage index o 2D echocardiogram at 2-4 days, 30days and at Month 6. o LVEF o LVESV o LVEDV o Cardiac dimensions (LVESD/ LVEDD) o Regional wall motion score index • If there is no difference between the MPC groups (using a test with alpha= 0.1) in the effect on LVESV then the pooled MPC group will be compared to the Placebo group for all functional parameters. o A subset analysis that corresponds to the stratification used during randomization will be performed. Stratification will be based on the following categories defined as time from onset of AMI symptoms to PCI: o $\leq$2 hours o >2 to $\leq$6 hours o >6 to $\leq$12 hours. • In addition, a subset analysis will be evaluated at the following ischemia duration time points: o $\leq$6 hours o >6 to $\leq$12 hours

	• NT-Pro-BNP serum levels (as a biomarker for heart failure) at baseline, days 2-4 and 30, and months 3, 6, 12 and 24 • Score changes for TIMI Flow Grade and TIMI Myocardial Perfusion Grade assessments at the following day 0 time points: o pre-PCI, o immediately post-PCI, o after approximately 50% of intracoronary infusion of investigational agent, o at completion of intracoronary infusion of investigational agent.
Safety Endpoints	All safety end points will be assessed from subject randomization through up to 24 months post investigational agent infusion: • SAE /AE rates • Occurrence of MACCE events including: o Cardiovascular death o Non-fatal myocardial infarction o Non-fatal stroke o Cardiac hospitalization due to heart failure • Target vessel (or other vessel) revascularization post index cardiac catheterization and new or worsening heart failure during the index hospitalization will be tracked as "Adverse Events of Special Interest". • Total number of subjects with documented ventricular arrhythmia (sustained and non-sustained VT/VF) throughout the study period. • Angina pectoris as defined by Canadian Cardiovascular Society (CCS) clinical clarification. • New York Heart Association (NYHA) Class. • Telemetry/48 hour Holter monitoring (during hospital admission and at 14 and 30 days, 3 and 6 months follow-up time points) with assessment of occurrence of ventricular arrhythmia. • TIMI Flow Grade and TIMI Myocardial Perfusion Grade following intracoronary infusion of the MPC cell solution compared with placebo • Physical examinations, monitoring of vital signs (heart rate, respiratory rate, BP, and temperature). • Results of clinical laboratory tests (hematology, serum chemistry, inflammatory markers), and immunogenicity assays; (flow cytometry Class I and Class II HLA percent reactivity % with specificity, antibovine and antimurine antibody analysis).

	AE will be collected after a subject has been randomized. The AE will be graded according to the protocol as "mild", "moderate", "severe" and will be classified with the Medical Dictionary for Regulatory Activities. An independent DSMB will review all safety and relevant clinical data at regular intervals in accordance with their charter. Based on its findings, the DSMB will make recommendations regarding study continuation, enrollment and/or study modification(s).
Feasibility Endpoint	Feasibility of the infusion of the investigational agent will monitored by measurement of TIMI flow and perfusion measurements prior to, during (after approximately 50% of total investigational agent volume infused) and following the investigational agent infusion after successful PCI and stenting.

Clinical Endpoints	Clinical Endpoints will be assessed throughout the index hospitalization as well as at outpatient visits at 14 and 30 days, and at 3, 6, 12, 18 and 24 months after the index cardiac catheterization procedure, including:
	• Occurrence of MACCE including:
	  o Cardiovascular death
	  o Non-fatal myocardial infarction
	  o Non-fatal stroke
	  o Cardiac hospitalization due to heart failure
	• Target vessel (or other vessel) revascularization post index cardiac catheterization and new or worsening heart failure during the index hospitalization will be tracked as "Adverse Events of Special Interest".
	• Total number of subjects with documented ventricular arrhythmia (sustained and non-sustained VT/VF) throughout the study period.
	• Angina pectoris as defined by Canadian Cardiovascular Society (CCS) clinical clarification.
	• Functional status will be classified by the NYHA criteria.

Planned Analysis of Efficacy and Safety	The primary efficacy analysis for LVESV will be performed using cMRI collected data. The secondary efficacy analyses for LVESV will be performed using ECHO data alone, as well as ECHO data as a substitute for missing cMRI data at baseline and/or at Month 6. In the latter case, a regression equation will be determined between measurements for LVESV-cMRI and LVESV-ECHO over a range of values. Whenever appropriate and based on LVESV-ECHO values generated using the regression equation, a LVESV-ECHO "corrected" value will be determined and used as

	a replacement for missing value for LVESV-cMRI. When all enrolled subjects have completed the study through Visit 9 (Month 6), an unblinded analysis of the safety and primary and secondary efficacy endpoints will be conducted. The primary and secondary efficacy analyses will be performed using data collected through Visit 9 (Month 6). Safety analyses will be performed on all available data through Visit 12 (Month 24) at the time of conduct of the efficacy analysis. In addition, the final safety analysis will be performed at 24 months for all patients. No additional efficacy data will be collected beyond Visit 9 (Month 6) except for cardiac biomarkers. **Blinded Study Personnel and Participants** Subjects, Site personnel, Investigators will remain blinded until after all safety follow-up is completed. The DSMB may choose to be unblinded. **Unblinded Study Personnel** Pre-specified unblinded clinical operations and biometrics team members at both the vendor and sponsor will have access to the unblinded efficacy results. These pre-specified unblinded team members will be identified prior to the analysis being conducted and they will not have any operational responsibility for the conduct of the study. An independent unblinded statistician from [redacted] will support the DSMB by providing Open and Closed Reports to the DSMB independent statistician based on the best available data and other information to the DSMB.
Inclusion Criteria	Subjects will be entered into this study only if they meet ALL of the following criteria: 1. Willing and able to understand and sign the Informed Consent Form (ICF). 2. Males or females ≥ 18 years. 3. Clinical symptoms consistent with AMI (pain, etc.) for a maximum of 12 hours from onset of symptoms to completion of PCI. 4. *De novo* anterior AMI [redacted]

	[redacted] 5. Successful revascularization of the culprit lesion [redacted] 6. If a female subject is of childbearing potential (i.e. not amenorrheic for 12 or more months and/or not surgically sterile), the subject must be willing to use a highly effective method of contraception (oral, injectable or implanted hormonal methods of contraception, placement of an intrauterine device [IUD] or intrauterine system [IUS], condom or occlusive cap with spermicidal foam/gel/film/cream/suppository, male sterilization, or true abstinence) for at least 16 weeks after investigational agent infusion. 7. Must be willing and able to return for required follow-up visits.
Exclusion Criteria	Subjects will not be enrolled into this study if they meet ANY of the following criteria: 1. Prior MI, known cardiomyopathy, or hospital admission for heart failure (HF). 2. Significant valvular disease (mitral or aortic valve regurgitation 3/4 classification as defined by ESC/ACC guidelines).

	3. Unsuccessful revascularization of culprit artery defined as TIMI 1 or 0 flow or residual diameter stenosis of ≥ 20% by on line QCA analysis. 4. Need for staged treatment of coronary artery disease, or other interventional or surgical procedures to treat heart disease [redacted] 5. Cardiogenic shock or hemodynamic instability within 24 hours prior to randomization, [redacted] 8. Prior PCI involving the LAD. 9. Malignancy within last 3 years from screening. The subject has had an active malignancy, within the past 3 years except for cervical carcinoma in situ or non-melanoma skin cancer that has been definitively treated. [redacted] 11. Pacemaker, ICD or any other contraindication for cMRI. This is inclusive of patients with an MRI compatible device that was implanted prior to the potential qualifying event. [redacted] 15. Known hypersensitivity to any radiographic contrast 16. Known hypersensitivity to dimethyl sulfoxide (DMSO),

	[redacted] 18. Prior participation in any other investigational drug trial in the past 30 days. 19. Pregnant or lactating women. [redacted]
Number of Treatment Arms	Eligible subjects will be randomized to one of three (3) parallel treatment arms: one of two (2) doses of investigational MPC agent or (saline) control. Subjects randomized to MPC product will be treated with either 12.5 million or 25 million cell dose.
Investigational Agent	The investigational MPC product is STRO-3 selected allogeneic MPCs, which are derived from adult bone marrow mononucleated cells that are culture-expanded and subsequently cryopreserved. [redacted]
Route of Administration	All subjects will receive investigational agent or placebo, suspended/dissolved in 100 mL 0.9% saline via intracoronary infusion following successful primary PCI.
Duration of Treatment	Subjects will receive treatment post successful PCI and stenting of the culprit LAD lesion.
Follow up Schedule	Each subject will be followed for up to 2 years after study intervention and will have assessments at screening, during study procedure, post procedure during hospitalization, 14 and 30 days, and again at 3, 6, 12, 18, and 24 months after intracoronary study treatment infusion. Refer to Table 2 Schedule of Assessments and Procedures.
Statistical Analysis	AE will be summarized descriptively by treatment group, using the incidence and frequency of subjects reporting any AE. The AE will be graded according to the protocol as “mild”, “moderate”, “severe” and will be classified with the Medical Dictionary for Regulatory Activities. All treatment-emergent AE (TEAE) will be presented by severity grade and by relationship to study therapy. Vital signs and clinical laboratory data will be summarized descriptively (mean, median, standard deviation, minimum, maximum) overall, and by treatment group. In addition, clinically significant changes in vital

	signs, laboratory parameters, and physical examination findings will be reported as appropriate and summarized. The following stratification for duration of cardiac ischemia will be performed to ensure balanced randomization across the treatment groups: ▪ ≤2 hours ▪ >2 hours to ≤6 hours ▪ >6 to ≤12 hours To detect a change from baseline to Month 6 treatment effect of 10.0 ml for LVESV (SD 14 ml), [redacted] as well as published clinical data[1- 3, 58, 59], with a two-sided 5% significance level and a power of 80%, a sample size of 105 subjects will be necessary, given the observed dropout rate of approximately 4%. Of these, approximately 70 will receive MPCs (35 to receive 12.5 M MPC and 35 to receive 25M MPC) and 35 will receive placebo and act as control subjects.

1.6 Assessments and Procedures

Table 2: Schedule of Assessments and Procedures

	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11	Visit 12	Early Term[r]
Study Day	**Day 0 AMI, Pre Study Infusion**	**Day 0 Immediate Post Study Infusion**	**6, 12, 18 Hours Post Study Infusion ± 1Hour**	**24 Hours Post Study Infusion ± 2Hours**	**2 - 7 Days Post Study Infusion (or Until Hosp D/C)**	**14 Days Post Study Infusion ± 3 Days**	**30 Days Post Study Infusion ± 7 Days**	**3 Mos. Post Study Infusion ± 7 Days**	**6 Mos. Post Study Infusion ± 14 Days**	**12 Mos. Post Study Infusion ± 14 Days**	**18 Mos. Post Study Infusion ± 30 Days**	**24 Mos. Post Study Infusion ± 30 Days**	
Assessment													
Informed consent and HIPAA	X												
Review of inclusion/exclusion criteria	X												
Medical and Surgical Histories[a]	X												
Physical examination[b]	X			X	X[l]	X	X	X	X	X		X	X
Concomitant medications, including vaccinations	X	X	X	X	X[l]	X	X	X	X	X	X	X	X
Vital signs[c]	X		X	X	X[l]	X	X	X	X	X		X	X
12-lead ECG	X	X		X	X[l]		X	X	X	X		X	X
Telemetry Monitoring		X	X	X	X[l]								
Basic Metabolic Profile[d]	X				X[h]	X	X	X	X	X		X	X
Troponin-I or Troponin-T	X		X	X	X[l]								
CK-MB	X		X	X	X[u]								
Non-fasting Lipid	X						X	X	X	X		X	X

Study Day	Visit 1 Day 0 AMI, Pre Study Infusion	Visit 2 Day 0 Immediate Post Study Infusion	Visit 3 6, 12, 18 Hours Post Study Infusion ± 1Hour	Visit 4 24 Hours Post Study Infusion ± 2Hours	Visit 5 2 - 7 Days Post Study Infusion (or Until Hosp D/C)	Visit 6 14 Days Post Study Infusion ± 3 Days	Visit 7 30 Days Post Study Infusion ± 7 Days	Visit 8 3 Mos. Post Study Infusion ± 7 Days	Visit 9 6 Mos. Post Study Infusion ± 14 Days	Visit 10 12 Mos. Post Study Infusion ± 14 Days	Visit 11 18 Mos. Post Study Infusion ± 30 Days	Visit 12 24 Mos. Post Study Infusion ± 30 Days	Early [r] Term
profile[e]													
hsC-Reactive Protein	X				X[h]	X	X	X	X	X		X	X
Hepatic Function Profile[f]	X				X[h]	X	X	X	X	X		X	X
Complete blood count with platelets and differential	X				X[h]	X	X	X	X	X		X	X
Flow cytometry Class I and Class II antibodies (% PRA) with specificity	X					X	X	X	X	X			X[o]
Anti-murine and Anti-bovine antibodies	X					X	X	X	X	X		X	X
NT-Pro Brain Natriuretic Peptide, type B	X				X[h]		X	X	X	X		X	X
Pregnancy test[g]	X							X					X
Primary PCI with stent placement	X												
2-D Echocardiogramm					X[h]		X		X				
Selective Coronary Angiogram of Target Vessel	X												
TIMI flow and perfusion measurements[j]	X	X											
QCA culprit vessel	X												

Study Day	Visit 1 Day 0 AMI, Pre Study Infusion	Visit 2 Day 0 Immediate Post Study Infusion	Visit 3 6, 12, 18 Hours Post Study Infusion ± 1Hour	Visit 4 24 Hours Post Study Infusion ± 2Hours	Visit 5 2 - 7 Days Post Study Infusion (or Until Hosp D/C)	Visit 6 14 Days Post Study Infusion ± 3 Days	Visit 7 30 Days Post Study Infusion ± 7 Days	Visit 8 3 Mos. Post Study Infusion ± 7 Days	Visit 9 6 Mos. Post Study Infusion ± 14 Days	Visit 10 12 Mos. Post Study Infusion ± 14 Days	Visit 11 18 Mos. Post Study Infusion ± 30 Days	Visit 12 24 Mos. Post Study Infusion ± 30 Days	Early [r] Term
Cardiac MRI [p]					X[h]		X		X				
Investigational Agent Infusion [q]	X												
Hospital Discharge with 48 hr. Holter					X								
Killip Class	X												
48 hour Holter Monitoring						X	X	X	X				
Canadian Cardiovascular Society Angina Classification					X[h]		X	X	X	X		X	X
NYHA classification					X[h]		X	X	X	X		X	X
Randomization	X												
AE/SAE Assessment [kk]	X	X	X	X	X[i]	X	X	X	X	X	X	X	X
Telephone assessment											X		

a. Previous Medical History includes medical, surgical, medication, alcohol, drug, and tobacco use, known renal and/or pulmonary disease recent immunizations/vaccinations, blood transfusions and number of pregnancies (females only)

b. Physical examination to include but not limited to examination of the cardiac, pulmonary, neurologic (including but not limited to mental status) and gastrointestinal systems as well as the measurement of weight. Height and body mass index (BMI) to be determined only at screening. At Visit 5 (Days 2-7 post study infusion), weight should only be measured on Target Day 3 (+/- 1 post study infusion).

c. Vital signs consist of blood pressure (BP), temperature, heart rate, and respiratory rate.

d. Basic Metabolic Profile (sodium, potassium, chloride, CO_2, blood urea nitrogen, glucose, creatinine, calcium, calculated GFR)

e. Non-fasting Lipid Panel (cholesterol, triglycerides, HDL, LDL)

f. Hepatic Function Profile (total protein, albumin, total bilirubin, direct bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase)
g. Urine Pregnancy testing at screening; serum pregnancy testing at follow-up study visits
h. Target Day 3 (+/- 1 day) post study infusion
i. Performed daily
j. During infusion of the Investigational Agent, TIMI flow and perfusion measurements should be evaluated and recorded prior to IA infusion, when approximately 50% of the Investigational Agent has been infused, and immediately post investigational agent infusion.
k. AE/SAE assessments should be collected from time of randomization
l. 12 lead ECG should be measured on Day 2 and prior to hospital discharge
m. 2D echo will be performed through 6 month follow-up period only. 2D echo will be performed without contrast
n. For subjects that receive Investigational agent and discontinue prior to Visit 9 (Month 6) cardiac MRI will not be obtained as part of the early termination visit.
o. Only for subjects that receive Investigational agent and discontinue prior to Visit 10 (Month 12)
p. cMRI will be performed through 6 month follow-up period only. Please refer to the study imaging manual for details on MRI contrast agents.
q. To be performed only if all inclusion/exclusion criteria are adequately satisfied.
r. An ET visit will include the following tests: Physical examination, record of concomitant medications, vital signs measurement, 12-lead ECG, basic metabolic profile, non-fasting lipid profile, hs C-reactive protein, hepatic function profile, CBC with differential and platelets, Flow cytometry anti-HLA Class I and Class II antibodies for subjects discontinued prior to visit 10 (Month 12), Anti-murine and Anti-bovine antibodies, NT-Pro BNP, serum pregnancy testing, Canadian Cardiovascular society Angina Classification , NYHA classification and NYHA classification. cMRI and ECHo are not required at an ET visit.

1.7 Glossary of Abbreviations

ACC	American College of Cardiology
AE	Adverse event
ALT	Alanine aminotransferase
AMI	Acute myocardial infarction
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase
BLA	Biologics license application
BMI	Body mass index
BP	Blood Pressure
BUN	Blood urea nitrogen
CABG	Coronary artery bypass graft
CBC	Complete blood count
CCS	Canadian Cardiovascular Society
CEC	Clinical Events Committee
CHF	Congestive heart failure
CFR	Coronary flow reserve
CK	Creatine kinase
CK-MB	Creatine kinase MB fraction
cMRI	Cardiac magnetic resonance imaging
CO_2	Carbon dioxide
COPD	Chronic obstructive pulmonary disease
CRF	Case report form
CRA	Clinical Research Associate
CRO	Clinical Research Organization
CV	Cardiovascular
DMSO	Dimethyl sulfoxide
DNA	Deoxyribonucleic acid
DSMB	Data and Safety Monitoring Board
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic case report form
EF	Ejection fraction
ESC	Executive Steering Committee
FDA	Food and Drug Administration
FEV	Forced Expiratory Volume
FU	Follow-up
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
GFR	Glomerular Filtration Rate
GTN	Glyceryl trinitrate
HF	Heart Failure
HIPAA	Health Insurance Portability and Accountability Act

HLA	Human Leukocyte Antigen
HR	Heart rate
IB	Investigator brochure
IC	Intracoronary
ICD	Implantable cardioverter defibrillator
ICF	Informed consent
IEC	Independent Ethics Committee
IND	Investigational new drug
IRB	Institutional Review Board
ITT	Intent-to-treat
IV	Intravenous
IVRS	Interactive voice response system
IWRS	Interactive web response system
LAD	Left anterior descending
LBBB	Left bundle branch block
LVAD	Left ventricular assist device
LVEDD	Left ventricular end-diastolic dimension
LVEDV	Left ventricular end-diastolic volume
LVEF	Left ventricular ejection fraction
LVESD	Left ventricular end-systolic dimension
LVESV	Left ventricular end-systolic volume
Mab	Monoclonal antibody
MACCE	Major adverse cardiac and cerebrovascular events
MB	Subunits of creatine kinase
[redacted]	[redacted]
MI	Myocardial infarction
MPC	Mesenchymal precursor cell
MSC	Mesenchymal stem cell
NT-Pro-BNP	N-terminal pro-brain natriuretic peptide, type B
NQWMI	Non-Q wave myocardial infarction
NTG	Nitroglycerin
NYHA	New York Heart Association
PBMCs	Peripheral blood mononuclear cells
PCI	Percutaneous coronary intervention
PCR	Polymerase chain reaction
PHI	Protected health information
PPP	Per-Protocol Population
PSP	Peak systolic pressure
PTE	Per Treatment Evaluable
QCA	Quantitative coronary analysis
SAE	Serious adverse event
SAP	Statistical analysis plan
SOC	System organ class
STEMI	ST-elevation myocardial infarction

SUSAR	Suspected unexpected serious adverse event reaction
TEAEs	Treatment emergent adverse events
TIA	Transient ischemic attack (cerebral)
TIMI	Thrombolysis In Myocardial Infarction
TTE	Transthoracic echocardiogram
UADE	Unanticipated adverse device effect
VF	Ventricular fibrillation
VT	Ventricular tachycardia

2. INTRODUCTION

2.1 Myocardial Infarction: The clinical risk remains high post the acute event

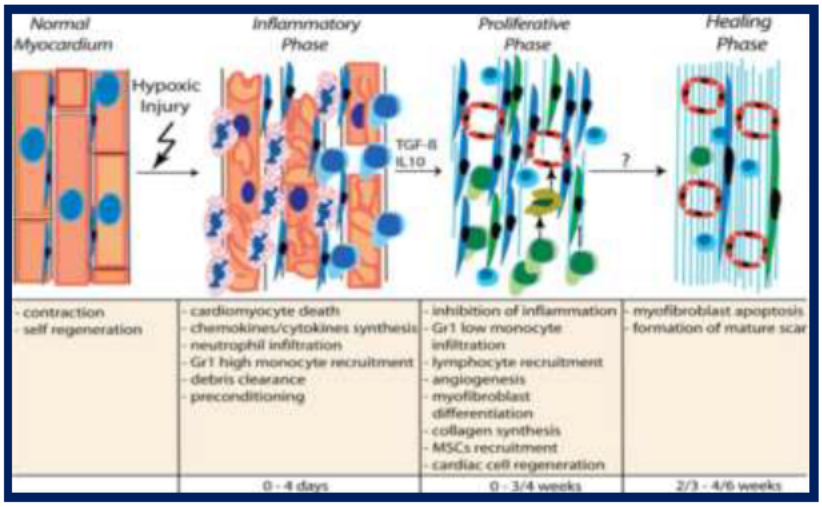
A recent update of US Medicare records was published that evaluated data involving 350,509 acute myocardial infarction (MI) hospitalization in patients ≥65 years who were discharged alive after their event.[3] Within the first year post the index event, 25.9% of the MI patients died with 50.5% re-hospitalized. In the month after a MI, the likelihood of death was 21 times higher and the likelihood of hospitalization was 12 times higher than among the general Medicare-age population. Similar one year mortality data have been published for patients post STEMI treated in Canada.[4] Clearly, despite important advances in standard of care therapies, there remains a large unmet clinical need to reduce death and re-hospitalization post MI. Stem cell therapy, especially with allogeneic cells, represents an innovative opportunity to explore early therapeutic approaches that would be adjunctive to coronary artery revascularization of the culprit lesion with the goal of reducing post MI adverse myocardial remodeling and major adverse cardiovascular events.[5-10]

In patients with acute ST-segment elevation myocardial infarctions (STEMI), there is a progression of myocardial injury that begins with the onset of cardiac ischemia and continues past the time of coronary reperfusion.[11] The adage that "Time is Tissue" remains a basic approach to patients with STEMI with the emphasis on timeliness of reperfusion therapy. The 2013 ACCF/AHA STEMI Management Guidelines state that "for patients with STEMI, an ideal first-medical contact to device time goal is 90 minutes or less".[12] This equates to a goal of onset of ischemic symptoms to device time of ≤120 minutes. When this cannot be achieved, the Guidelines further emphasize that "Reperfusion therapy should be administered to all eligible patients with STEMI with symptom onset within the prior 12 hours". Because the pathophysiologic processes that include necrosis and apoptosis evolve over time, it is important to consider the duration of myocardial ischemia as an important variable in subsequent analyses of the natural history of myocardial infarctions with and without specific interventions.[13-16]

Over the past decade, much investigation in acute myocardial ischemia has centered on the evaluation of the processes that result in induction of inflammatory cytokines as well as their effect on acute and chronic cardiac remodeling post-infarction.[17-21] During the acute phase of myocardial ischemia, physiologic insults (increased mechanical stretch, oxidative stress, and hypoxia) occur that rapidly induce cytokines (e.g., TNF-α and/or IL-6) leading to enhanced/accelerated myocyte necrosis and apoptosis resulting in decreased left ventricular LV function and clinical compromise.[17] This is followed by cytokine amplification with transmigration of macrophages and neutrophils. During the chronic phase post-MI, the

activation of matrix metalloproteinases and their inhibitors contribute to the laying down of collagen and wound repair. Elaboration of angiogenic and progenitor cell mobilization factors contributes to wound healing. The following figure summarizes the phases as well as timeframe of these processes.[17]

Figure 1: Cellular and Molecular Mechanisms Follow Myocardial Infarction



2.2 Allogeneic Mesenchymal Cells

Human bone marrow contains at least two different stem cell populations, i.e. haematopoietic stem cells, which give rise to all mature blood elements, and non- MPCs that give rise to stromal cells referred to as mesenchymal stem cells (MSCs) or bone marrow stromal stem cells.[22] MSCs are undifferentiated, pluripotent cells that possess the ability to differentiate into a variety of cells such as osteoblasts, chondroblasts, adipocytes, skeletal muscle cells and cardiomyocytes.[23,24] The therapeutic applications of MSCs have been the topic of much research over the past decade.

The study Sponsor has developed a process to immunoselect the MPCs from adult bone marrow mononuclear cells and then expand these cells in culture to produce allogeneic MPCs. Unlike MSCs, which are obtained through density centrifugation and plastic adherence of bone marrow, MPCs consist of a large number of pure, homogenous, concentrated mesenchymal cells with defined characteristics and minimal lot to lot variability. These expanded cells have been shown to retain the mesenchymal cell capacity for differentiation into bone, cartilage, and adipose tissue in vitro and to regenerate bone in-vivo.[24] In addition, they possess potent immunosuppressive and anti-inflammatory properties as well as neovascularization capabilities. MPCs have

established biological activity, consistent characterisation, enhanced purity and potency, and are immediately available ("off the shelf") for allogeneic use.

Please refer to the Investigator's Brochure (IB) for further information.

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2.4 Cardiac Magnetic Resonance Imaging (cMRI): Assessment of Myocardial Ischemia, Viability, and Microvascular Obstruction

Cardiac magnetic resonance imaging (cMR) is a useful validated tool to assess multiple structural and physiologic parameters in the setting of acute STEMI as well as its long term follow-up. [2,3,32-34] The following are the cMRI assessments that will be performed in the AMICI trial.

2.4.1 Myocardium at Risk (Area of Ischemia)

Ischemic volume will be measured by the edematous volume using T2-weighted images and a triple inversion recovery fast spin echo sequences protocol. [35,36]

2.4.2 Infarct Size

The size of infarcted myocardium will be measured as the volume of tissue exhibiting late contrast enhancement. [32,37]

2.4.3 Infarct Size to Area at Risk Ratio

This reflects the percent of the myocardium at risk that ultimately is infarcted. It is calculated as the ratio of the volume of infarcted myocardium (late contrast enhancement) to the volume of edematous myocardium (the ischemic volume determined by T-2 weighted images).

2.4.4 Microvascular Obstruction (MVO)

After completion of the primary PCI for acute STEMI, restoration of blood flow at both the epicardial coronary artery level (as assessed by angiographic TIMI Flow Grade) and myocardial (tissue) level yields the best clinical outcomes. [32,38] This points to the critical role of the myocardial microvasculature in determining outcomes despite the relief of epicardial stenosis (even in the presence of TIMI 3 flow). Cardiac MRI evaluation of MVO is conducted by assessment for lack of late contrast-enhanced myocardial imaging (i.e. central dark zone) after revascularized STEMI within the infarction. [37]

It is important to emphasize that studies using radiologic contrast angiography have demonstrated that restoration of epicardial flow does not necessarily lead to restoration of tissue level or microvascular perfusion. [39] The TIMI Myocardial Perfusion Grade (TMPG) has been shown to be a multivariate predictor of mortality in acute STEMI at 2 years of follow-up. It permits risk stratification even within epicardial TIMI grade 3 flow. Indeed, despite achieving epicardial patency with normal TIMI grade 3 flow, those STEMI patients whose microvasculature fails to open have a 7-fold increase in mortality compared with those patients with both TIMI grade 3 flow in the epicardial artery and no evidence of microvascular obstruction. Among acute STEMI patients undergoing primary PCI, post-PCI TMPG correlates with cMR measurements of MVO and infarct size.[39] The combined use of both metrics in a comprehensive assessment of microvascular integrity and infarct size following STEMI adds to an improved understanding of future therapeutic strategies.

[redacted]

[redacted]

2.6 Rationale

Healing of an MI is complicated by the need for viable myocytes at the peri-infarct margin to undergo compensatory hypertrophy in order to increase pump function in response to the loss of infarcted tissue.[40,41] This initiates a process termed "cardiac remodeling," which is characterized by apoptotic loss of hypertrophied myocytes, expansion of the initial infarct area, progressive collagen replacement, that collectively result in the development of heart failure.[42-45] The Sponsor has recently advanced the hypothesis that hypertrophied cardiac myocytes undergo apoptosis because the endogenous capillary network cannot provide the compensatory increase in perfusion required for cell survival. [46]

Vascular network formation is the end result of a complex process that begins in the prenatal period with induction of vasculogenesis. Cells that can differentiate into endothelial and smooth muscle elements also exist in adult bone marrow[47-49] and can induce vasculogenesis in ischemic tissues.[50-52] The Sponsor has identified a specific population of MPCs derived from human adult bone marrow which has phenotypic and functional characteristics of vascular pericyte precursor cells that provide the building blocks necessary for arteriogenesis. Since recent observations have suggested that a second compensatory response of viable cardiomyocytes is to proliferate and regenerate following injury, [53,54] it is theoretically possible that further increase in the infarct bed capillary network through regulated neovascularization could result in increased regenerative capacity of the heart leading to improvement in myocardial function.

Administration of MPCs resulted in significant improvement in several key parameters of myocardial function in rodents following AMI[55] In particular, epicardial injection of MPCs resulted in a dose-dependent arteriogenesis at the infarct border zone. This arteriogenesis was coupled with echocardiographic improvement in EF as well as restoration of near normal contractility and LV end-diastolic pressure. Additionally, MPCs have been shown to secrete cytokines in a paracrine manner that could augment their direct trans differentiation potential.[56,57]

The use of the 'off-the-shelf' allogeneic MPCs derived from healthy donors with the Sponsor's proprietary process requires no cell culture and can be infused directly following recanulation of the involved artery and reperfusion of the infarcted tissue during a time period of myocardial

infarction. The use of allogeneic donor cells obviates the need for second catheterization, hospitalization or anesthetic for treatment. Therapy can be provided without the delay necessitated by days or weeks of cell culture, commonly observed with the use of mesenchymal stem cells obtained from bone marrow.

No clinical efficacy studies of allogeneic MPCs in cardiovascular indications have been completed to date, but in an ongoing phase 2 study HF-AB002 (conducted by the sponsor), a scheduled interim analysis was performed after all study subjects had a minimum of 12 months of follow-up. In this interim review of data for the Phase 2 study, transendocardial injections of MPCs in subjects with chronic heart failure was found to be feasible and safe. Treatment of subjects with allogeneic MPCs was not associated with a clinically significant immune response. Treatment was associated with significant reduction of MACCE and heart failure disease-specific endpoints, with the latter demonstrating a positive effect of 150 M MPC. Beneficial effects were also seen on LV remodeling and functional exercise capacity with this dose of MPCs. The results show a positive effect of MPCs on clinically relevant findings of heart failure treatment response.

[redacted]

3. STUDY HYPOTHESIS

MPCs when administered intracoronary immediately after successful PCI with stenting in patients with first time acute anterior STEMI will result in amelioration of the early post-event inflammatory response and subsequent fibrotic scarring as well as promote the process of neo-angiogenesis in tissue where an ischemic condition exists or is developing. The net result will be:

- decreased infarct size by short term protection of at-risk myocardium
- increased long term salvage of myocardium resulting in decreased adverse left ventricular (LV) remodeling.

4. STUDY OBJECTIVES

4.1 Primary Objective

The primary objective of this study is to determine the safety and feasibility of intracoronary allogeneic, immuno-selected, bone marrow-derived Stro3 MPC delivery in the treatment of subjects with STEMI undergoing primary percutaneous coronary intervention of the LAD coronary artery.

4.2 Secondary Objectives

- To explore a dose-response effect of intracoronary delivered MPC in the treatment of subjects with an anterior wall STEMI on LV remodelling, microvascular obstruction, and the relationship between time from onset of ischemic symptoms to primary PCI.
- To determine the effect of intracoronary delivery of allogeneic immunoselected, bone marrow-derived MPC on infarct size reduction in the treatment of subjects with STEMI undergoing primary PCI of the LAD coronary artery.
- [redacted]

4.3 Study Design

This is a prospective, double blind, randomized, placebo-controlled, dose finding study that will enroll approximately 105 subjects with *de novo* anterior STEMI due to a lesion involving LAD coronary artery who undergo primary PCI at approximately 25 clinical study sites.

This study will compare two doses of MPCs and a placebo control group. Study subjects will be randomly assigned in 1:1:1 fashion to receive either 12.5 M or 25 M MPCs or placebo (saline). Each group will have approximately 35 subjects.

Potential subjects will be approached by the site investigator prior to PCI and must sign an informed consent form before initiation of the cardiac catheterization procedure in order to participate in this trial. Following successful and uneventful PCI and stenting of the culprit LAD lesion, the subjects will be randomized. The randomization and treatment assignment will be obtained from an IVRS/ IWRS. The following stratification for duration of cardiac ischemia will be performed to ensure balanced randomization across the treatment groups:

- ≤2 hours
- >2 hours to ≤6 hours
- >6 to ≤12 hours.

Eligible subjects will receive intracoronary delivery of the assigned treatment infused via a microcatheter into the stented culprit artery. The subjects randomized to MPCs will be infused at an infusion rate of 2 ml/min over approximately 60 minutes, including line flush [$2.5x10^5$ MPCs/min (12.5 M), $5.0x10^5$ MPCs/min (25 M)]. The subjects randomized to placebo will be infused placebo solution at 2 mL/min over approximately 60 minutes, including line flush (0 MPCs/min). Due to the presence of a catheter in the coronary arteries for this period of time, anticoagulants should be given as clinically indicated. The MPC product (12.5M and 25M MPCs) and the placebo solution will be diluted in 100mL 0.9% saline solution prior to infusion. The Sponsor will provide all sites with blinded treatment cryobags or cryovials, which contain the different doses of MPCs or placebo solution.

An IC bolus of GTN/ NTG (100-200mcg) should be administered (blood pressure permitting) prior to TIMI flow assessments during the investigational agent infusion period as well as after completion of the investigational agent infusion and immediately prior to the final coronary angiographic imaging.

After approximately 50% of the intracoronary infusion of investigational agent has been completed, an angiographic determination of coronary flow will be performed. The following guidelines will be used to determine if the remaining investigational agent should be infused:

- The study infusion should be continued if either TIMI 2 or TIMI 3 flow is present in the absence of ALL of the following:
  - Sustained hypotension not responsive to fluid administration;
  - Clinical signs/symptoms indicating an acute cerebrovascular event;
  - Re-elevation of ST-segments if previously resolved with PCI;
  - Onset of the subject's symptoms of myocardial ischemia unresponsive to appropriate interventions;
  - Two episodes of sustained ventricular tachycardia/ventricular fibrillation requiring cardioversion (infusion can continue if a single episode of sustained VT/VF requiring cardioversion occurred).

If for any reason, the site investigator withdraws a randomized subject prior to infusion of the investigational agent, the reason for early termination and data from the screening visit will be entered into the eCRF by the study site. The subject will not remain in the study. If for any reason, a subject's study infusion is halted due to safety considerations, the subject will remain in the study. A subject who prematurely withdraws from the study post study infusion will remain in the study.

Evaluation for safety will be performed for up to 24 months post infusion. Subjects will undergo cardiac magnetic resonance imaging (cMRI) and 2-D echocardiography (ECHO), Holter monitoring, clinical evaluation and laboratory testing.

cMRI, ECHO monitoring will be performed at 2-7 days post infusion of study agent (MPC or Placebo), as well as at Day 30 and at Month 6 after the procedure. Holter monitoring will be performed at 14 and 30 days, 3 and 6 months after the procedure. Clinical evaluation and laboratory testing will be performed at 6, 12, 18 and 24 hours post infusion of study agent (MPC or Placebo), during the index hospitalization as well as at 14 and 30 days and 3, 6, 12, 18 and 24 months after the procedure as outlined in Table 2 Schedule of Assessments and Procedures.

An independent DSMB will review all relevant acute peri-procedural data, SAE, other AE, and efficacy data (if requested) periodically dependent on subject enrollment and advise the ESC regarding the progression of the study. The ESC will consist of the Principal Investigator, site investigators and representatives of and advisors to the Sponsor.

A CEC will review appropriate source documents and adjudicate (blinded per a priori procedure) all MACCE defined as cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, or cardiac hospitalization due to heart failure. Target vessel (or other vessel) revascularization post index cardiac catheterization and new or worsening heart failure during the index hospitalization will be tracked as "Adverse Events of Special Interest" rather than MACCE.

Blinded Study Personnel and Participants

Subjects, Site personnel, Investigators will remain blinded until after all safety follow-up is completed. The DSMB may choose to be unblinded.

Unblinded Study Personnel

Pre-specified unblinded clinical operations and biometrics team members at both the vendor and sponsor will have access to the unblinded efficacy results.

These pre-specified unblinded team members will be identified prior to the analysis being conducted and they will not have any operational responsibility for the conduct of the study.

An independent unblinded statistician from [redacted] will support the DSMB by providing Open and Closed Reports to the DSMB independent statistician based on the best available data and other information to the DSMB.

The DSMB safety reviews to assess the frequency of total MACCE will be performed after the initial 15, 30, 60, and 90 subjects have been observed at Day 30 post the index cardiac catheterization. The final safety analysis will be performed at 24 months for all patients.

5. SELECTION AND WITHDRAWAL OF SUBJECTS

The study population will consist of an 'all-comers' subject population with a *de novo* anterior AMI who are undergoing primary PCI with stent placement within 12 hours after onset of symptoms, who meet all the inclusion and none of the exclusion study criteria. Enrollment and treatment is anticipated to include approximately 105 subjects at approximately 25 clinical sites. The subjects will be of any race and of either gender.

[redacted]

5.1.1 Inclusion Criteria

Subjects will be entered into this study only if they meet ALL of the following criteria:

1. Willing and able to understand and sign the Informed Consent Form (ICF).
2. Males or females ≥ 18 years.
3. Clinical symptoms consistent with AMI (pain, etc.) for a maximum of 12 hours from onset of symptoms to percutaneous coronary intervention (PCI).
4. *De novo* anterior Acute Myocardial Infarct (AMI) [redacted]
5. Successful revascularization of the culprit lesion [redacted]
6. If a female subject is of childbearing potential (i.e., not amenorrheic for 12 or more months and/or not surgically sterile), the subject must be willing to use highly effective method of contraception (oral, injectable or implanted hormonal methods of contraception, placement of an intrauterine device [IUD] or intrauterine system [IUS], condom or occlusive cap with spermicidal foam/gel/film/cream/suppository, male sterilization, or true abstinence)) for at least 16 weeks after investigational agent infusion.
7. Must be willing and able to return for required follow-up visits.

5.1.2 Exclusion Criteria

Subjects will not be enrolled into this study if they meet ANY of the following criteria:

1. Prior MI, known cardiomyopathy, or hospital admission for heart failure (HF).
2. Significant valvular disease (mitral or aortic valve regurgitation 3/4 classification as defined by ESC/ACC guidelines).
3. Unsuccessful revascularization of culprit artery defined as TIMI 1 or 0 flow or residual diameter stenosis of ≥ 20% by on line QCA analysis.
4. Need for staged treatment of coronary artery disease, or other interventional or surgical procedures to treat heart disease [redacted]
5. Cardiogenic shock or hemodynamic instability within 24 hours prior to randomization, [redacted]
8. Prior PCI involving the LAD
9. Malignancy within last 3 years from screening. The subject has had an active malignancy, within the past 3 years except for cervical carcinoma in situ, or non-melanoma skin cancer that has been definitively treated.

[redacted]

11. Pacemaker, ICD or any other contra-indication for cMRI. This is inclusive of patients with an MRI compatible device that was implanted prior to the potential qualifying event.

[redacted]

[redacted]

18. Prior participation in any other investigational drug trial in the past 30 days.

[redacted]

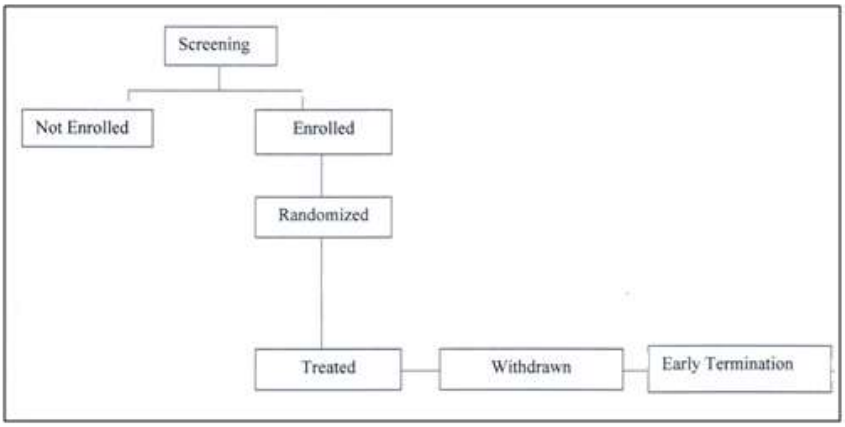
5.2 Subject Withdrawal

Subjects may withdraw from the study at any time, for any reason, without penalty, or prejudice to his or her future medical care. The investigator also has the right to withdraw subjects from the study in the event of intercurrent illness, adverse events, administrative, or other reasons.

5.3 Withdrawal Procedures

In all cases, the reason(s) for withdrawal must be recorded on the eCRF. If a subject prematurely withdraws from the study post-study infusion for any reason, the investigator must make every effort to perform the evaluations described for the Early Termination visit. Since the ICF states that subjects that prematurely withdraw post study-infusion for any reason may also be contacted by telephone for follow-up safety information for up to 24 months post study infusion, unless the subject also specifically withdraws consent for this communication all subjects may also be contacted by telephone.

Figure 2: Randomization/Withdrawal



The randomization number assigned to a withdrawn subject will not be re-used.

Subjects who sign consent and are not randomized will be considered screen failures.

If during the course of the study a subject chooses to revoke his/her written authorization for the use and disclosure of Protected Health Information [PHI] (per HIPAA privacy ruling or other country and/or region specific law), the subject will then be withdrawn from the study as well (i.e., participation in this study is contingent upon an "active" written PHI use, collection, and disclosure authorization and only safety data will be collected as required by applicable laws. PHI collected prior to the date that the subject revokes his/her written authorization may still be used. In the event of a subject's withdrawal, the investigator will promptly notify the medical monitor or designee and will make every effort to complete the assessments as indicated above for subjects who prematurely discontinue from the study. All withdrawn subjects will be followed until resolution of any AEs or until the unresolved AEs are judged by the investigator to have stabilized.

5.4 Early Termination of Study

If the sponsor, the investigator, or a regulatory authority discover conditions arising during the conduct of the study that indicate that the study should be halted or that the study center should be closed, this action may be taken after prompt, appropriate consultation between the Sponsor and the investigator(s). Conditions that may warrant termination of the study include, but are not limited to, the following:

- The discovery of an unexpected, serious, or unacceptable risk to the subjects enrolled in the study or if, in the sponsor's judgment there are no further potential benefits to be achieved from the study.
- A decision on the part of the sponsor to suspend or discontinue testing, evaluation or development of the investigational product.

Study termination and follow-up will be performed in compliance with the conditions set forth in the International Conference on Harmonization of Technical Requirements of Pharmaceuticals for Human Use Guideline (ICH E6) and relevant applicable regulations.

5.4.1 Data Safety and Monitoring Board Overview

An independent DSMB will be established and is the primary external data and safety group for the study. All members shall have experience and expertise in cardiovascular clinical trials and/or stem cell therapy. DSMB members may not participate in the study as principal or co-

investigators, study subject physicians or in any other capacity that might compromise their privileged position on the DSMB.

The DSMB will periodically review study safety and efficacy data and make recommendations to the ESC Chair and Sponsor. The ESC has the responsibility to accept, reject or to modify DSMB recommendations. A separate charter outlining the operations of the DSMB will be developed. The DSMB will meet as specified in the charter.

5.4.2 Executive Steering Committee

The ESC will meet periodically by teleconference to monitor subject enrollment, clinical site progress, and protocol compliance according to the charter. The responsibilities of the ESC are to: (a) maintain contact with study investigators to stimulate enrollment and ensure high quality data; (b) implement major protocol changes in response to the advice of the DSMB and agreement of Sponsor; (c) help develop dissemination of the results of the study through publications and presentations at major meetings.

5.4.3 Clinical Event Committee

The responsibilities of the CEC are to perform a review of appropriate source documents and to perform a blinded adjudication of all MACCE defined as cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, or cardiac hospitalization due to heart failure. In addition, the CEC will review all cases of target vessel (or other vessel) revascularization post index cardiac catheterization and new or worsening heart failure during the index hospitalization. These will be designated as "Adverse Events of Special Interest" rather than MACCE.

The CEC committee may also review cardiac events not considered MACCE or "Adverse Events of Special Interest" including, but not limited to hospitalization for unstable angina, hospitalization for resuscitated cardiac arrest, and transient ischemic attack. The definition of heart failure will be described in the CEC charter. The individuals who will serve on the committee will be independent of the Sponsor, the DSMB, the ESC, the clinical study sites and the trial's investigators. The committee will consist of cardiologists with prior experience with adjudication of cardiac events in clinical trials. No CEC member will be present during any study procedures, and all CEC members will be blinded to the subject treatment assignments. The CEC will meet as needed to adjudicate adverse events and outcomes data for each subject enrolled. A charter will be developed to outline the CEC process and procedures.

6. STUDY PROCEDURES

6.1 Study Visits

6.1.1 Enrollment and Eligibility

The investigator or his/her designee, such as the study coordinator, will notify the Sponsor or its CRO designee of each potential subject, if possible. Once a subject is determined to be eligible and has provided informed consent, the site will call the IVRS for randomization. Each qualified subject will be randomized to one of three parallel treatment arms, 12.5 or 25 x 10^6 MPCs or to the sterile saline control arm. All subjects will receive a single infusion via intracoronary administration at a rate of 2 mL/min for approximately 60 minutes, including line flush.

Evaluations performed at each study visit and visit windows are summarized below. If a subject misses a visit, all efforts should be made to reschedule the missed visit within the allocated visit window.

6.1.1.1 Visit 1: Screening/Day of Infusion (Day 0), Pre Study Infusion

Informed consent will be obtained prior to any study specific procedures.

The following procedures will be performed prior to infusion of the study investigational agent:

- Informed consent
- Review of inclusion and exclusion criteria
- Review of medical and surgical history, including determination of:
  - Medication history, including recent vaccinations and/or immunizations
  - Blood product transfusion history
  - Pregnancy history (females only)
  - Tobacco, drug, alcohol use history
  - Renal disease
  - Pulmonary disease
- Physical examination to include but not limited to examination of the cardiac, pulmonary, neurologic (including but not limited to mental status) and gastrointestinal systems as well as the measurement of height, weight, and body mass index (BMI).
- Recording of concomitant medications including vaccinations
- Vital signs (BP, temperature, heart rate, and respiratory rate)
- 12 lead ECG

- Basic metabolic profile [sodium, potassium, chloride, carbon dioxide (CO_2), blood urea nitrogen (BUN), glucose, creatinine and calcium, calculated glomerular filtration rate (GFR)]
- Troponin I (or T)
- Creatine kinase and MB fraction (CK-MB)
- Non-fasting lipid profile (cholesterol, triglycerides, HDL and LDL)
- High Sensitive (hs) C-reactive protein (CRP)
- Hepatic function profile (total protein, albumin, alkaline phosphatase, alanine transaminase, aspartate aminotransferase, direct bilirubin, total bilirubin)
- Complete Blood Count (CBC) with differential and platelets
- Flow cytometry anti-HLA Class I and Class II antibodies (%PRA) with specificity
- Anti-murine and anti-bovine antibodies
- NT-Pro BNP [brain natriuretic peptide, type B]
- Urine pregnancy test (females not amenorrheic for the previous 12 months and/or not surgically sterile)
- Record details of PCI (i.e. angiogram findings, stent details)
- Selective coronary angiogram of target vessel
- TIMI flow and perfusion measurement
- QCA analysis of the culprit vessel (to determine diameter residual stenosis and procedural success)
- Randomization
- Preparation of study investigational agent
- Commencement of infusion of study investigational agent within 30 minutes after completion of PC
- Killip Class I
- AE/SAE assessment.

6.1.1.2 Visit 2: Day of Infusion (Day 0), Immediately Post Study Infusion

- Recording of concomitant medications including vaccinations
- 12 Lead ECG
- Telemetry monitoring
- Record study investigational agent infusion details
- TIMI flow and perfusion measurements
- AE/SAE assessment.

6.1.1.3 Visit 3: Six, Twelve, Eighteen Hours Post Study Infusion (± 1 hour)

- Recording of concomitant medications including vaccinations
- Vital signs (BP, temperature, heart rate, respiratory rate)
- Telemetry monitoring
- Troponin I (or T)
- Creatine kinase and MB fraction
- AE/SAE assessment.

6.1.1.4 Visit 4: Twenty-four Hours Post Study Infusion (± 2 hours)

- Physical examination to include but not limited to examination of the cardiac, pulmonary, neurologic (including but not limited to mental status) and gastrointestinal systems as well as weight. New physical examination findings of any system will be noted. In the event of abnormal neurological findings, subjects will require a neurological consult.
- Recording of concomitant medications including vaccinations Vital signs (BP, temperature, heart rate and respiratory rate)
- 12 Lead ECG
- Telemetry monitoring
- Troponin I (or T)
- Creatine kinase and MB fraction
- AE/SAE assessment.

6.1.1.5 Visit 5: Two thru Seven Days Post Study Infusion

- Daily physical examination to include but not limited to examination of the cardiac, pulmonary, neurologic (including but not limited to mental status) and gastrointestinal systems. New physical examination findings of any system will be noted. In the event of abnormal neurological findings, subjects will require a neurological consultation.
- Recording of concomitant medications including vaccinations
- Daily vital signs (BP, temperature, heart rate and respiratory rate)
- 12 Lead ECG on Day 2 and prior to hospital discharge
- Daily telemetry monitoring
- Daily Troponin I (or T)
- Daily creatine kinase MB fraction
- Daily AE/SAE assessment
- Hospital Discharge on Day 4-7 with outpatient 48 hour Holter monitor
- **The target date for the following assessment is Day 3 post study infusion ±1 day:**

- Basic Metabolic Profile (sodium, potassium, chloride, carbon dioxide (CO_2), blood urea nitrogen (BUN), glucose, calculated GFR, creatinine and calcium)
- hs C-reactive Protein (CRP)
- Hepatic function profile (total protein, albumin, alkaline phosphatase, alanine transaminase, aspartate aminotransferase, direct bilirubin, total bilirubin)
- CBC with differential and platelets
- NT-Pro Brain Natriuretic Peptide, type B
- 2D echocardiogram
- Cardiac MRI
- Canadian cardiovascular society angina classification (CCS)
- NYHA Classification
- Weight.

6.1.1.6 Visit 6: Fourteen Days Post Study Infusion (± 3 days)

- Physical examination to include but not limited to examination of the cardiac, pulmonary, neurologic (including but not limited to mental status) and gastrointestinal systems as well as weight. New physical examination findings of any system will be noted. In the event of abnormal neurological findings, subjects will require a neurological consultation.
- Recording of concomitant medications including vaccinations
- Vital signs (BP, temperature, heart rate and respiratory rate)
- Basic metabolic profile (sodium, potassium, chloride, carbon dioxide (CO_2), blood urea nitrogen (BUN), glucose, calculated GFR, creatinine and calcium)
- hs C-reactive protein (CRP)
- Hepatic function profile (total protein, albumin, alkaline phosphatase, alanine transaminase, aspartate aminotransferase, direct bilirubin, total bilirubin)
- CBC with differential and platelets
- Flow cytometry anti-HLA Class I and Class II antibodies (%PRA) with specificity
- Anti-murine and anti-bovine antibodies
- 48 hour Holter monitor
- AE/SAE assessment.

6.1.1.7 Visit 7: Thirty Days Post Study Infusion (± 7 days)

- Physical examination to include but not limited to examination of the cardiac, pulmonary, neurologic (including but not limited to mental status) and gastrointestinal systems as well as weight. New physical examination findings of any system will be noted. In the event of abnormal neurological findings, subjects will require a neurological consultation.

- Recording of concomitant medications including vaccinations
- Vital signs (BP, temperature, heart rate and respiratory rate)
- 12 Lead ECG
- Basic metabolic profile (sodium, potassium, chloride, carbon dioxide (CO_2), blood urea nitrogen (BUN), glucose, calculated GFR, creatinine and calcium)
- Non-fasting Lipid Profile
- hs C-reactive protein (CRP)
- Hepatic function profile (total protein, albumin, alkaline phosphatase, alanine transaminase, aspartate aminotransferase, direct bilirubin, total bilirubin)
- CBC with differential and platelets
- Flow cytometry anti-HLA Class I and Class II antibodies (%PRA) with specificity
- Anti-murine and anti-bovine antibodies
- NT-Pro BNP [Brain Natriuretic Peptide, type B]
- 2D echocardiogram
- Cardiac MRI
- 48 hour Holter monitor
- Canadian cardiovascular society angina classification (CCS)
- NYHA Classification
- AE/SAE assessment.

6.1.1.8 Visit 8: Three Months Post Study Infusion (± 7 days)

- Physical examination to include but not limited to examination of the cardiac, pulmonary, neurologic (including but not limited to mental status) and gastrointestinal systems as well as weight. New physical examination findings of any system will be noted. In the event of abnormal neurological findings, subjects will require a neurological consultation.
- Recording of concomitant medications including vaccinations
- Vital signs (BP, temperature, heart rate and respiratory rate)
- 12 Lead ECG
- Basic metabolic profile (sodium, potassium, chloride, carbon dioxide (CO_2), blood urea nitrogen (BUN), glucose, calculated GFR, creatinine and calcium)
- Non-fasting Lipid Profile
- hs C-reactive protein (CRP)
- Hepatic function profile (total protein, albumin, alkaline phosphatase, alanine transaminase, aspartate aminotransferase, direct bilirubin, total bilirubin)
- CBC with differential and platelets

- Flow cytometry anti-HLA Class I and Class II antibodies (%PRA) with specificity
- Anti-murine and anti-bovine antibodies
- NT-Pro BNP [brain natriuretic peptide, type B]
- Serum pregnancy test (females not amenorrheic for the previous 12 months and/or not surgically sterile)
- 48 hour Holter monitor
- Canadian cardiovascular society angina classification (CCS)
- NYHA Classification
- AE/SAE assessment.

6.1.1.9 Visit 9: Six Months Post Study Infusion (± 14 days)

- Physical examination to include but not limited to examination of the cardiac, pulmonary, neurologic (including but not limited to mental status) and gastrointestinal systems as well as weight. New physical examination findings of any system will be noted. In the event of abnormal neurological findings, subjects will require a neurological consultation.
- Recording of concomitant medications including vaccinations
- Vital signs (BP, temperature, heart rate and respiratory rate)
- 12 Lead ECG
- Basic metabolic profile (sodium, potassium, chloride, carbon dioxide (CO_2), blood urea nitrogen (bun), glucose, calculated GFR, creatinine and calcium)
- Non-fasting Lipid Profile
- hs C-reactive protein (CRP)
- Hepatic Function profile (total protein, albumin, alkaline phosphatase, alanine transaminase, aspartate aminotransferase, direct bilirubin, total bilirubin)
- CBC with differential and platelets
- Flow cytometry anti-HLA Class I and Class II antibodies (%PRA) with specificity
- Anti-murine and anti-bovine antibodies
- NT-Pro BNP [brain natriuretic peptide, type B]
- 2D Echocardiogram
- Cardiac MRI
- 48 hour Holter monitor
- Canadian cardiovascular society angina classification (CCS)
- NYHA Classification
- AE/SAE assessment.

6.1.1.10 Visit 10: Twelve Months Post Study Infusion (± 14 days)

- Physical examination to include examination of the cardiac, pulmonary, neurologic (including but not limited to mental status) and gastrointestinal systems as well as weight. New physical examination findings of any system will be noted. In the event of abnormal neurological findings, subjects will require a neurological consultation.
- Recording of concomitant medications including vaccinations
- Vital signs (BP, temperature, heart rate and respiratory rate)
- 12 Lead ECG
- Basic metabolic profile (sodium, potassium, chloride, carbon dioxide (CO_2), blood urea nitrogen (bun), glucose, calculated GFR, creatinine and calcium)
- Non-fasting Lipid Profile
- hs C-reactive protein (CRP)
- Hepatic function profile (total protein, albumin, alkaline phosphatase, alanine transaminase, aspartate aminotransferase, direct bilirubin, total bilirubin)
- CBC with differential and platelets
- Flow cytometry anti-HLA Class I and Class II antibodies (%PRA) with specificity
- Anti-murine and anti-bovine antibodies
- NT-Pro BNP [brain natriuretic peptide, type B]
- Canadian cardiovascular society angina classification (CCS)
- NYHA Classification
- AE/SAE assessment.

6.1.1.11 Visit 11: Eighteen Months Post Study Infusion (± 30 days)

- Telephone follow-up
- Recording of concomitant medications including vaccinations
- AE/SAE assessment.

6.1.1.12 Visit 12: Twenty Four Months Post Study Infusion (± 30 days)

- Physical examination to include but not limited to examination of the cardiac, pulmonary, neurologic (including but not limited to mental status) and gastrointestinal systems as well as weight. New physical examination findings of any system will be noted. In the event of abnormal neurological findings, subjects will require a neurological consultation.
- Recording of concomitant medications including vaccinations
- Vital signs (BP, temperature, heart rate and respiratory rate)
- 12 Lead ECG

- Basic metabolic profile (sodium, potassium, chloride, carbon dioxide (CO_2), blood urea nitrogen (bun), glucose, calculated GFR, creatinine and calcium)
- Non-fasting Lipid Profile
- hs C-reactive protein (CRP)
- Hepatic function profile (total protein, albumin, alkaline phosphatase, alanine transaminase, aspartate aminotransferase, direct bilirubin, total bilirubin)
- CBC with differential and platelets
- Anti-murine and anti-bovine antibodies
- NT-Pro BNP [brain natriuretic peptide, type B]
- Canadian cardiovascular society angina classification (CCS)
- NYHA Classification
- AE/SAE assessment
- Complete study exit information.

6.1.1.13 Early Termination Visit

For subjects who are withdrawn from the study post study infusion and prior to completion of the study at Month 24, an Early Termination Visit will be scheduled. The following procedures will be performed at the Early Termination Visit:

- Physical examination to include, but not limited to, examination of the cardiac, pulmonary, neurologic (including but not limited to mental status), and gastrointestinal systems as well as weight. New physical examination findings of any system will be noted. In the event of abnormal neurological findings, subjects will require a neurological consult.
- Recording of concomitant medications including vaccinations
- Vital signs (BP, temperature, heart rate and respiratory rate)
- 12-lead ECG
- Basic metabolic profile (sodium, potassium, chloride, bicarbonate, BUN, glucose, calculated GFR, creatinine, and calcium)
- Non-fasting Lipid Profile
- hs C-reactive protein (CRP)
- Hepatic function profile (total protein, albumin, alkaline phosphatase, ALT, AST, direct bilirubin, and total bilirubin)
- CBC with differential and platelets
- Flow cytometry anti-HLA Class I and Class II antibodies (PRA%) only for subjects that discontinue prior to Visit 10 (Month 12)

- Anti-murine and anti-bovine antibodies
- NT-Pro BNP [brain natriuretic peptide, type B]
- Serum pregnancy testing
- Canadian Cardiovascular Society Angina Classification
- NYHA Classification
- Adverse event and SAE assessment.

6.2 Study Monitoring

All aspects of the study should be conducted in accordance with Good Clinical Practice (GCP) as described in ICH E6 and all other applicable regulations.

The Sponsor and/or its designated CRO will monitor the study. Monitoring will be performed by qualified individuals designated by the Sponsor and in accordance with the protocol, GCP and standard operating procedures for compliance with applicable regulations. The investigators agree to allow the monitors direct access to source documents.

In addition, the study may be evaluated by representatives from regulatory agencies, who will also be allowed access to study documents. The investigators will promptly notify the Sponsor or its designee of any audits or inspections they have scheduled with any regulatory agency/authority.

6.3 Follow-up/Lost to Follow-up

Vigorous attempts will be made to obtain follow-up evaluations for all study subjects who are enrolled in the study.

If necessary, appointment reminders will be sent by mail by the study coordinator before the scheduled follow-up visit and telephone contact will be attempted in the event that a study subject fails to attend a scheduled follow-up visit.

A minimum of three telephone calls will be made to the subject and if no response, a certified letter will be sent to the subject in an attempt to obtain follow-up information.

7. STUDY TREATMENTS

7.1 Study Infusion Continuation and Halt Guidelines

Procedure-related cardiac arrhythmias will be handled according to current 2004 ACC/AHA/ESC practice guidelines for management of subjects with ventricular arrhythmias and the prevention of sudden cardiac death will be implemented.

After approximately 50% of the intracoronary infusion of investigational agent has been completed, an angiographic determination of coronary flow will be performed. The following guidelines will be used to determine if the remaining investigational agent should be infused:

1. The study infusion should be continued if either TIMI 2 or TIMI 3 flow is present in the absence of ALL of the following:
2. Sustained hypotension not responsive to fluid administration;
3. Clinical signs/symptoms indicating an acute cerebrovascular event;
4. Re-elevation of ST-segments if previously resolved with PCI;
5. Onset of the patient's symptoms of myocardial ischemia unresponsive to appropriate interventions;
6. Two episodes of sustained ventricular tachycardia (VT)/ventricular fibrillation (VF) requiring cardioversion (infusion can continue if a single episode of sustained VT/VF requiring cardioversion occurred).

If TIMI flow is 1 or 0 at this assessment, regardless of associated symptoms listed above, the infusion of investigational agent must be terminated.

7.2 Definition of Adverse Event of TIMI 1 or 0 flow

If the study infusion procedure is terminated due to a TIMI 1 or 0 flow in the absence of clinically evident symptoms, this must be reported as an AE. The appropriate term to record in the CRF is 'Cardiac procedure complication.

7.3 Investigational Agent

7.3.1 Investigational Agent Labeling

The content of the coded treatment cryovials (MPC and saline placebo) will not be known to the participating centers, subject representatives of the Sponsor, or data management organization, and the code will not be broken until after the database of the study has been locked by the CRO.

[redacted]

[redacted]

[redacted]

[redacted]

7.3.4 Investigational Agent/Control Agent Handling and Accountability

All study product accountability records including records of randomization assignment will be maintained by the investigator or qualified designee, stored in a secure location and reviewed during monitoring visits by the assigned CRA/monitor.

[redacted]

[redacted]

7.4 Control Agent

7.4.1 Description of Control Agent

The control placebo agent is sterile saline. In addition to the coded MPC agent, the coded study placebo agent will also be provided by the Sponsor and prepared in similar volume and similar

cryovials, as applicable, as the MPC product so as to help make it as indistinguishable from the investigational MPC product as best as possible.

7.5 Blinding and Randomization

This is a double blinded study. Each subject will be blinded to his/her assigned treatment. Study blinding will be maintained as described below.

Blinded Study Personnel and Participants

Subjects, Site personnel, Investigators will remain blinded until after all safety follow-up is completed. The DSMB may choose to be unblinded.

Unblinded Study Personnel

Pre-specified unblinded clinical operations and biometrics team members at both the vendor and sponsor will have access to the unblinded efficacy results.

These pre-specified unblinded team members will be identified prior to the analysis being conducted and they will not have any operational responsibility for the conduct of the study.

An independent unblinded statistician from the CRO will support the DSMB by providing Open and Closed Reports to the DSMB independent statistician based on the best available data and other information to the DSMB.

Subjects that are admitted within a maximum of 12 hours after onset of ischemic cardiac symptoms who are experiencing a *de novo* anterior MI and qualify based on inclusion/exclusion criteria will be approached for enrollment. Eligible subjects will be randomized to receive one of three possible intracoronary treatments: Investigational product at 12.5 M or 25.0 M allogeneic MPCs or saline placebo control.

Randomization will occur after informed consent has been obtained and the PCI with stenting of the culprit LAD coronary artery lesion has been successfully completed (residual TIMI Flow Grade 3 or 2, residual diameter stenosis <20% by QCA, uncomplicated primary PCI).

The randomization and treatment assignment will be obtained from an IVRS/ IWRS.

The following stratification for duration of cardiac ischemia will be performed to ensure balanced randomization across the treatment groups:

- ≤2 hours
- >2 hours to ≤6 hours
- >6 to ≤12 hours.

After randomization has been performed, each subject will receive a unique identification number that will include site and subject identifiers.

7.5.1 Un-blinding Procedure

The study blind should not be broken except in a medical emergency (where knowledge of the test material received would affect the treatment of the emergency) for regulatory requirement (e.g., suspected unexpected serious adverse reactions (SUSARs)), and for the unblinded analysis of efficacy and preliminary safety once all subjects have completed the 6-month visit. If an emergency un-blinding becomes necessary, the investigator should notify the Sponsor or Medical Monitor, as soon as possible.

7.5.2 Concomitant Therapy

All subjects will receive standard post-therapy care guided by standard practices at the study center. In the event of procedure-related cardiac arrhythmias, current ACC/AHA/ESC practice guidelines for management of subjects with ventricular arrhythmias and the prevention of sudden cardiac death will be implemented. All other investigational agents or therapies are prohibited for the duration of this study.

All concomitant medications administered to study subjects will be recorded on the eCRF.

8. ASSESSMENT OF EFFICACY

Feasibility of the infusion of the investigational agent will monitored by measurement of TIMI flow and perfusion prior to, during, and following the investigational agent infusion after successful PCI and stenting.

8.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the change in LVESV as assessed by cardiac MRI from baseline to 6 months post investigational agent infusion for each MPC treatment group compared with control.

8.2 Secondary Efficacy Endpoints

- The change in LVESV as assessed by 2D-echocardiography from baseline to 6 months post investigational agent infusion.
- The change in relative infarct size as assessed by late contrast enhancement MRI (% infarct volume/total LV tissue volume) from baseline to 6 months post investigational agent infusion.
- Additional functional efficacy endpoints will be assessed with the following diagnostic studies:
    - Cardiac MRI at 2-4 days, 30 days and at Month 6.
        - LVEF
        - LVESV
        - LVEDV
        - Left ventricular wall thickness and thickening in all segments including infarct area
        - Regional wall motion score
        - Myocardial MVO measured as reduced signal intensity in the region of interest
        - MI size measured in the region of interest as late contrast enhancement
        - Myocardial salvage index
    - 2D echocardiogram at 2-4 days, 30 days and at Month 6.
        - LVEF
        - LVESV
        - LVEDV
        - Cardiac dimensions (LVESD/ LVEDD)
        - Regional wall motion score index
    - If neither MPC arm is found to be better than the placebo arm and there is no difference between the MPC groups (using the ANCOVA test with alpha=.1) in the effect on LVESV then the pooled MPC group will be compared to the placebo group for all functional parameters.
    - A subset analysis that corresponds to the stratification used during randomization will be performed. Stratification will be based on the following following categories defined as time from onset of AMI symptoms to PCI:
        - ≤2 hours
        - >2 hours to ≤6 hours
        - >6 to ≤12 hours.

- In addition, a subset analysis will be evaluated at the following ischemia duration time points:
  - ≤6 hours
  - >6 to ≤12 hours.
- NT-Pro-BNP serum levels (as measurement biomarker for heart failure) at baseline, days 2-4 and 30 and months 3 6, 12 and 24
- Score changes for TIMI Myocardial Flow Grade and Perfusion assessments at the following day 0 time points:
  - pre-PCI,
  - immediately post-PCI,
  - after approximately 50% of intracoronary infusion of investigational agent,
  - at completion of intracoronary infusion of investigational agent.

8.3 Clinical Endpoints

Clinical Endpoints will be assessed throughout the index hospitalization as well as at outpatient visits at 14 and 30 days, and at 3, 6, 12, 18 and 24 months after the index cardiac catheterization procedure, including:

- Occurrence of MACCE:
  - Cardiovascular death
  - Non-fatal myocardial infarction
  - Non-fatal stroke
  - Cardiac hospitalization due to heart failure
- Target vessel (or other vessel) revascularization post index cardiac catheterization and new or worsening heart failure during the index hospitalization will be tracked as "Adverse Events of Special Interest".
- Total number of subjects with documented ventricular arrhythmia (sustained and non-sustained VT/VF) throughout the study period.
- Angina pectoris as defined by CCS clinical clarification.
- Functional status will be classified by the NYHA criteria.

9. ASSESSMENT OF SAFETY

9.1 Safety Endpoints

All safety endpoints will be assessed from subject randomization through up to 24 months post investigational agent infusion:

- SAE / AE rates
- Occurrence of MACCE including:
  - Cardiovascular death
  - Non-fatal myocardial infarction
  - Non-fatal stroke
  - Cardiac hospitalization due to heart failure
- Target vessel (or other vessel) revascularization post index cardiac catheterization and new or worsening heart failure during the index hospitalization will be tracked as "Adverse Events of Special Interest".
- Total number of subjects with documented ventricular arrhythmia (sustained and non-sustained VT/VF) throughout the study period.
- Angina pectoris as defined by CCS clinical clarification.
- NYHA Class.
- Telemetry/48 hour Holter monitoring (during hospital admission and at 14 and 30 days, 3 and 6 months follow-up time points) with assessment of occurrence of ventricular arrhythmia.
- TIMI flow and perfusion measurements following intracoronary infusion of the MPC cell solution compared with placebo.
- Physical examinations, monitoring of vital signs (heart rate, respiratory rate, BP, and temperature).
- Results of clinical laboratory tests (hematology, serum chemistry, inflammatory markers), and immunogenicity assays; (flow cytometry Class I and Class II HLA percent reactivity % with specificity, antibovine and antimurine antibody analysis).

AE will be collected after a subject has been randomized. The AE will be graded according to the protocol as "mild", "moderate", "severe" and will be classified according to MedDRA.

An independent DSMB will review all safety and relevant clinical data at regular intervals in accordance with their charter. Based on its findings, the DSMB will make recommendations regarding study continuation, enrollment and/or study modification(s).

The primary safety analysis will be performed on the following safety and feasibility parameters up to 30 days post-treatment:

- TIMI flow prior to, during (approximately 50% of total infusion of investigational agent) and following infusion of investigational agent after successful PCI.
- SAE/AE rates.
- Results of clinical laboratory tests (including hematology, serum chemistry, inflammatory markers, flow cytometry anti-HLA Class I and Class II percent reactivity with specificity, antibovine and antimurine antibody analysis).
- Infusion procedure monitoring of vital signs (heart rate, respiratory rate, BP, and temperature.

9.2 Adverse Events

Each AE should be assessed by the investigator to establish its seriousness, severity and causality (relationship to the investigational product).

9.3 Definitions

Adverse Event (AE) is defined as any untoward medical occurrence in a subject who was treated with an investigational product, and does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign, symptom, or disease, whether or not related to the investigational product.

Serious Adverse Event (SAE) is defined as any untoward medical occurrence that:

- results in death,
- is life-threatening,
- requires inpatient hospitalization or prolongation of existing hospitalization,
- results in persistent or significant disability/incapacity,
- is a congenital anomaly/birth defect, or
- is medically important*

* "Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience, when based on appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition." (CFR 312.32).

Expectedness: An SAE is considered "unexpected" if it is not listed in the IB or is not listed at the specificity or severity that has been observed. The Sponsor is responsible for assessing expectedness of SAE.

Suspected Unexpected Serious Adverse Event reactions (SUSAR) is defined as a SAE event occurring in a subject in an interventional study that is assessed as both causally related to the suspect product under clinical investigation and unexpected per the IB.

9.4 Relationship to Study Product

For each AE, the relationship to the study drug must be recorded as either related (there is a reasonable possibility of a causal relationship between the event and the investigational agent) or not related (there is not a reasonable possibility of a causal relationship between the event and the investigational agent). In general, a causal relationship will be assigned when facts, evidence, or arguments exist to support the causal relationship.

When assessing a relationship between investigational agent and an adverse event, the following parameters are to be considered:

- The causal relationship is reasonable on the basis of clinical judgment and given the currently available data.
- A temporal relationship exists between treatment with the investigational agent or protocol-specified procedures and the AE.
- A biologic plausibility of relationship is present.
- Any underlying concurrent illness and/or therapies the subject has received are considered.

9.5 Relationship to Study Procedure

For each AE, the relationship to the Investigational Agent delivery procedure must be recorded as either **related** (there is a reasonable possibility of a causal relationship between the event and the study procedure) or **not related** (there is not a reasonable possibility of a causal relationship between the event and the study procedure).

9.6 Severity of Adverse Events

The intensity of each event will be rated by the investigator or if needed using the following per protocol severity classifications:

Severity	**Definition**
Mild:	AEs are transient, require no special treatment, and do not interfere with subject's daily activities.
Moderate:	AEs introduce a low level of inconvenience or concern to the subject and may interfere with daily activities, but are usually ameliorated by simple therapeutic measures.
Severe:	AEs interrupt a subject's usual daily activities and typically require systemic drug therapy or other treatment. A severe AE is not necessarily serious; for instance, a migraine headache lasting for several hours may be considered severe but not serious. Action taken will be categorized as none, study drug discontinued, dose modified, required concomitant medication, required procedure, or other.

9.7 Procedures for Adverse Event Reporting

AE will be collected only after a subject has been randomized.

All AE (including MACCE), will be recorded by the investigator or designee as part of the study participant's medical history records and on the appropriate case report form. The investigator or designee will evaluate the relationship of the AE to both the investigational agent and study procedure as related, not related, or unknown, and will record the findings, including all pertinent details of the event on the eCRF.

The investigator will take appropriate measures to ensure the subject's well-being and document these interventions on the appropriate eCRF. The DSMB will review these events.

To maintain a consistent and thorough approach to the collection, documentation and assessment of AE, it is essential that investigators provide the Sponsor with the highest level of medical understanding of each event. This means that when describing an event, medical diagnosis is preferred to a list of symptoms. If a diagnosis can be made, which organizes or explains multiple symptoms or a cascade of events, the diagnosis will become the AE and should replace multiple symptoms in the eCRF and study records.

9.8 Protocol- Specified Serious Adverse Events

For the purposes of this study, SAE that are primary endpoint events will not be reported individually in an expedited manner. These protocol-specified SAE will be monitored by the DSMB. The DSMB will monitor the occurrence of MAACE, all-cause mortality and adverse

events of special interest (target vessel revascularization and new or worsening HF during the index hospitalization) throughout the study. The DSMB will review all safety data periodically in a blinded fashion and may request unblinding of the data, as needed. If aggregate analysis indicates that the events are occurring more frequently in the MPC treatment group this will be reported as appropriate (e.g. IND safety report, CIOMs, etc.).

The following is a list of events that will not be reported in an expedited manner:

- Death (Cardiovascular/Non-Cardiovascular/Unknown)
- Myocardial infarction
- Hospitalization for Unstable Angina
- Hospitalization for other angina/chest pain
- Hospitalization for heart failure
- Percutaneous or Surgical Coronary Revascularization
- Percutaneous or Peripheral Arterial Revascularization
- Transient Ischemic Attack
- Stroke.

9.9 Reporting Requirements

All SAE reported or observed during the trial, whether protocol defined or not and whether or not attributable to the investigational agent, must be reported to [redacted] within 24 hours of the knowledge of the occurrence (this refers to any AE that meets any of the aforementioned serious criteria). To report the SAE, the investigator or designee will complete the SAE form electronically in the eCRF. When the form is completed, [redacted] Safety personnel will be notified electronically and will retrieve the form. If the event meets serious criteria, and it is not possible to access the eCRF, the investigator or designee will send an e-mail to [redacted] Safety at [redacted] or call the [redacted] SAE hotline (phone number listed below) and fax the completed paper SAE form to [redacted] (fax number listed below) with 24 hours of awareness. When the eCRF becomes available, the SAE information must be entered within 24 hours of the system becoming available. [redacted] Safety personnel are available for SAE reporting on a 24-hour basis. Reports are reviewed during normal business hours of the receiving office.

Safety Contact Information:
[redacted] Clinical Safety
[redacted]
[redacted]
[redacted] USA
[redacted] SAE hotline – North America/Asia Pacific:
[redacted]
Facsimile: [redacted]
e-mail: [redacted]
[redacted] SAE hotline – Europe/Israel:
Telephone: [redacted]
Facsimile: [redacted]
e-mail: [redacted]

The investigator must continue to follow the subject until the SAE has subsided or until the condition becomes chronic in nature, stabilizes (in the case of persistent impairment), or the subject dies. Within 24 hours of receipt of follow-up information, the investigator or designee must update the SAE form electronically in the EDC system for the study and submit any supporting documentation (e.g., subject discharge summary or autopsy reports) to [redacted] Safety personnel via fax or e-mail. If it is not possible to access the eCRF, refer to the procedures outlined above for initial reporting of SAEs.

The Sponsor and/or designated CRO personnel will be available to answer questions and to assist site personnel in documenting SAEs and completing the SAE eCRF.

All SAE that are considered unexpected and related to the study product will be reported by the Sponsor or its designee as a 15-day report to the Regulatory Authorities as applicable and to all participating investigators.

SAEs that are considered unexpected, related to the study and are life threatening or result in death will be reported by the Sponsor or its designee to the regulatory authorities as applicable, and to all participating investigators as a 7-day report.

Each investigator must notify the Institutional Review Board (IRB)/ Ethics Committee (EC) responsible for reviewing the study at their site of all 15-day or 7-day safety reports required by local regulations and shall provide the Sponsor or its designee with written confirmation of said IRB/EC notification.

9.10 Pregnancy Reporting

If the subject becomes pregnant during the study, the investigator should report the pregnancy to the Sponsor, or its representative, within 24 hours of being notified. [redacted] Safety personnel will then forward the Exposure in Utero form to the investigator for completion. The subject should be followed by the investigator until completion of the pregnancy and continue to be monitored for duration of the study. If the pregnancy ends for any reason before the anticipated date, the investigator should notify the Sponsor. At the completion of pregnancy, the investigator will document the outcome of pregnancy. If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (i.e., postpartum complication, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly), then the investigator should follow reporting procedures for an SAE.

10. ASSESSMENT OF FEASIBILITY

10.1 Feasibility Endpoint

Feasibility of the infusion of the investigational agent will monitored by measurement of TIMI Flow prior to, during (approximately 50% of total investigational agent volume infused), and following the investigational agent infusion after successful PCI and stenting.

11. STATISTICAL CONSIDERATION

11.1 Introduction

The objective of this study is to determine the safety and feasibility of IC allogeneic immuno-selected, bone marrow-derived Stro3 MPC delivery in the treatment of subjects with STEMI undergoing primary PCI of the LAD coronary artery.

11.2 Statistical Methods

The primary efficacy analysis will use an ANCOVA model with baseline LVESV as covariate and alpha=0.05 to test for a difference of change in LVESV from baseline to Month 6 between each MPC arm separately and the placebo arm. If neither MPC arm is found to be better than the placebo arm and there is no difference between the MPC groups (using the ANCOVA test with alpha= 0.1) in the effect on LVESV, then the pooled MPC group will be compared to the placebo group for all functional parameters.

All other statistical tests will be considered to be exploratory (post-hoc) unless a pre-specified hypothesis exists in the statistical analysis plan (SAP), which will be finalized prior to any analysis. All statistical tests will be two-sided and statistical significance will be assessed with

respect to a nominal p-value ≤0.05. Any deviations from the planned analyses will be documented and justified in the final clinical/statistical study report.

The primary efficacy analysis for LVESV will be performed using cMRI collected data. The secondary efficacy analyses for LVESV will be performed using ECHO data alone, as well as ECHO data as a substitute for missing cMRI data at baseline and/or at Month 6.

In the latter case, a regression equation will be determined between measurements for LVESV-cMRI and LVESV-ECHO over a range of values. Whenever appropriate and based on LVESV-ECHO values generated using the regression equation, a LVESV-ECHO "corrected" value will be determined and used as a replacement for missing value for LVESV-cMRI.

When all enrolled subjects have completed the study through Visit 9 (Month 6), an unblinded analysis of the safety and primary and secondary efficacy endpoints will be conducted.

The primary and secondary efficacy analyses will be performed using data collected through Visit 9 (Month 6). In addition, safety analyses will be performed on all available data through Visit 12 (Month 24) at the time of conduct of the efficacy analysis. In addition, the final safety analysis will be performed at 24 months for all patients.

No additional efficacy data will be collected beyond Visit 9 (Month 6) except for cardiac biomarkers.

11.3 General Considerations

All clinical test results will be listed and summarized by treatment and time with appropriate descriptive statistics (number of observations, mean, median, standard deviation, minimum, and maximum) for continuous measures. Nominal and ordinal scale measures will be summarized with frequency tables, relative risk, and percentages, as appropriate.

11.4 Analysis Populations

The four populations, Safety, Intent-to-Treat (ITT), Per Protocol (PPP) and Full Analysis Population (FAP), are defined below.

11.4.1 Safety Population

The Safety set will include all ITT subjects who received the study treatment. In the event that a subject receives treatment other than what was assigned, safety analyses will be conducted according to the treatment that the subject actually received.

11.4.2 Intent-to-Treat Population

The set of Intent-to-Treat (ITT) subjects will include all subjects who are randomly assigned to a treatment at screening, regardless of whether or not the subject receives the study treatment.

11.4.3 Per-Protocol Population

The PPP will include ITT subjects who do not have major protocol violations, and have at least one post-treatment efficacy and safety evaluation.

11.4.4 Full Analysis Population

The Full Analysis Population will include all subjects who are randomized, have undergone PCI and had infusion of study agent (MPCs or Placebo) initiated.

11.5 Determination of Sample Size

To detect a treatment effect of 10.0 ml for LVESV (SD 14 ml), [redacted] as well as published clinical data [1-3, 58,59], with a two-sided 5% significance level and a power of 80%, a sample size of 105 subjects will be necessary, given the observed dropout rate of approximately 4%. Of these, approximately 70 will receive MPCs (35 to receive 12.5 M MPC and 35 to receive 25M MPC) and 35 will receive placebo and act as control subjects.

11.6 Background, Demographic and Concomitant Medications

Demographic data, medical history, concomitant disease and concomitant medication will be summarized by means of descriptive statistics (n, mean, SD, median, minimum and maximum) or frequency tables, stratified by treatment.

11.7 Protocol Deviations

Deviations from the protocol including violations of inclusion/exclusion criteria will be assessed as “minor” or “major”. Deviations will be defined prior to un-blinding.

11.8 Efficacy and Feasibility Analyses

Where appropriate, 95% confidence intervals for treatment differences in key feasibility measures will be constructed. Analysis of covariance (ANCOVA) may be used where appropriate to adjust for baseline differences in key continuous feasibility outcome measures and also take the site and the time from onset of AMI symptoms to PCI as covariates in the ANCOVA model. For non-normally distributed measures, the Wilcox-Mann-Whitney test or analysis of variance ANOVA of rank transformed data may be used as an alternative. For categorical measures, relative risks and nominal 95% confidence intervals will be constructed to assess strength of association. The Cochran-Mantel-Haeszel test (CMH) controlled by site and the time from the onset of AMI symptom to PCI will be used for the treatment differences. The primary feasibility analysis will be performed on the FA population, and confirmatory based on PP population.

The primary and secondary efficacy analyses will be performed on ITT, FA, and PP populations. Analysis of clinical endpoints will be performed on all analysis populations.

11.9 Safety Analyses

Review of safety tables, listings and figures will be performed by the medical monitor or designee. The safety tables will allow a view of changes from baseline in findings from 12-lead ECGs, vital signs, clinical laboratory values, and adverse events. No statistical testing will be executed for safety measures.

In this safety study with a limited sample size and projected high subject exclusion rate, the safety analysis will be performed on the Safety population. These analyses will include categorization of events per study phase (before and after cell infusion or assigned treatment) and event attribution as appropriate to the study phase. All analyses will include those at baseline, to 2 weeks post-index procedure.

Safety analyses will be performed on all available data through Visit 12 (Month 24) at the time of conduct of the efficacy analysis. In addition, the final safety analysis will be performed at 24 months for all patients.

11.10 Timing of Planned Analyses

Primary and Secondary Efficacy Analysis:
Analysis of efficacy will occur once all subjects have completed the 6-month visit.

Feasibility analysis:
Feasibility analysis based on TIMI flow will be concurrent with the analysis of efficacy described above.

Initial Safety Follow Up:
Preliminary analysis of safety will be concurrent with the analysis of efficacy described above.

Long Term Safety Follow up:
Analysis of long-term safety will occur once all subjects have completed the 24-month visit.

12. QUALITY CONTROL AND QUALITY ASSURANCE

The Sponsor shall implement and maintain quality control and quality assurance procedures with written standard operating procedures to ensure that the study is conducted and data are generated, documented, and reported in compliance with the protocol, GCP, and applicable regulatory requirements. This study shall be conducted in accordance with the provisions of the Declaration of Helsinki (October 1996) and all revisions thereof, and in accordance with applicable regulations and with the ICH guidelines on GCP (ICH E6).

13. REGULATORY OBLIGATIONS

13.1 Institutional Review Board (IRB)/ Ethics Committee (EC) Approval

Prior to enrollment of subjects into the study, as required by relevant regulations, the protocol, and informed consent form will be reviewed and approved by an appropriate IRB/EC. By signing the Statement of Investigator Form (FDA 1572 or equivalent), the investigator assures that all aspects of the institutional review will be conducted in accordance with current federal regulations and ICH. A letter documenting the IRB/EC approval must be received by the sponsor prior to the initiation of the study. Amendments to the protocol will be subject to the same review and approval requirements as the original protocol.

The investigator shall promptly notify the IRB/EC of any SAE, or any other information that may affect the safe use of the drug during the course of the study.

13.2 Protocol Compliance

Except for a change that is intended to eliminate an apparent immediate hazard to a study subject, the protocol shall be conducted as described. Protocol violations must be reported immediately to the Sponsor or its representative(s) as well as the governing IRB/EC and relevant regulatory authority as required.

13.3 Changes to the Protocol

The investigator may not deviate from the protocol without a formal protocol amendment having been established and approved by an appropriate IRB/EC, and relevant regulatory authority if required, except when necessary to eliminate immediate hazards to the subject or when the change(s) involve only logistical or administrative aspects of the study. Any deviation may result in the subject having to be withdrawn from the study and rendering that subject non-evaluable.

13.4 Informed Consent

Each subject must sign the study-specific informed consent form to enroll as a participant in the study. This consent form will comply with all applicable regulations governing the protection of human subjects. The basic elements of informed consent are specified in the ICH Guideline for GCP (E6).

13.5 Source Documents

During the study, the investigator will maintain adequate records for the study, including medical records, records detailing the progress of the study for each subject, laboratory reports, study worksheets/subject questionnaires, signed informed consent forms, drug disposition records, correspondence with the IRB/EC/Competent Authority, AE reports, and information regarding subject discontinuation and completion of the study.

13.6 Case Report Form Completion

All data obtained during this study should be entered on the eCRFs promptly. All source documents from which eCRF entries are derived should be placed in the subject's medical records.

13.7 Financial Disclosures

In accordance with the US Code of Federal regulations, Title 21, Part 54, the investigator will provide the Sponsor or its designee sufficient and accurate information on financial interests (proprietary or equity interests, payments exclusive of clinical study costs) to allow complete disclosure to regulatory authorities. The investigator shall promptly update this information with any relevant changes that occur during the course of the study and for a period of 1 year following the completion of the study.

13.8 Termination of the Study

If the Investigator, Medical Monitor, ESC or DSMB becomes aware of conditions or events that suggest a possible study related hazard to subjects if the study continues, they may recommend to the Sponsor that the study be terminated after appropriate consultation between the relevant parties. The decision to terminate the study remains with the Sponsor. The study may also be terminated early at the Sponsor's discretion in the absence of such a finding.

Conditions that may warrant termination by the Sponsor may include, but are not limited to:

- The discovery that in the opinion of the Sponsor poses an unexpected, significant, or unacceptable risk to the subjects enrolled in the study;
- A decision on the part of the Sponsor to suspend or discontinue development of the test material for any reason.

13.9 Retention of Essential Documents

All records and documents pertaining to the study including, but not limited to, those outlined above will be maintained by the investigator for at least a period of (or longer depending upon the local Regulatory Agency requirements): (a) 2 years after last approval of the product; (b) 5 years after non-approval of the Biologics License Application (BLA); or (c) 2 years after termination of investigational agent development program. In order to avoid any possible errors, the investigator will contact the Sponsor prior to the destruction of any study records. The investigator will promptly notify the Sponsor in the event of accidental loss or destruction of any study records.

13.10 Confidentiality

All study findings and documents will be regarded as confidential. The investigator and members of his/her research team must not disclose such information without prior written approval from the Sponsor.

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