Investigator Led Study of Intravenous Milrinone in Heart Failure with Preserved Ejection Fraction (HFpEF).

IV Mil for HFpEF

Protocol No: **MilHFpEF-IV-02**

**Version:** 1

**Date:** 14th May 2019

**Investigator Led**

**CHANGES**

**Investigator led not sponsor**

**Alfred will own data, Cardiora will have access to results upon request**

**8 patients, 6 active, 2 control. 25mcg IV Mil.**

**INVESTIGATOR SIGNATURE PAGE**

By signing this Protocol, the Investigator acknowledges and agrees:

* The Protocol contains all necessary details for conducting the study. The Investigator will conduct this study as detailed herein, in compliance with International Conference on Harmonisation (ICH) Good Clinical Practice (GCP)1 and the applicable regulatory requirements, and will make every reasonable effort to complete the study within the time designated.
* The Protocol and all relevant information on the drug relating to pre-clinical and prior clinical experience will be made available to all physicians, nurses and other personnel who participate in the conducting of this study. The Investigator will discuss this material with them to assure that they are fully informed regarding the drug and the conduct of the study.
* This document contains information that is privileged or confidential. As such, it may not be disclosed unless specific prior permission is granted in writing by The Investigator or such disclosure is required by federal or other laws or regulations. Persons to whom any of this information is to be disclosed must first be informed that the information is confidential. These restrictions on disclosure will apply equally to all future information supplied, which is indicated as privileged or confidential.
* The conduct and results of this study will be kept confidential. The results of this study may be published. Upon completion of the Study it is the intention of the parties to prepare a joint publication regarding or describing the Study and all the results there from and both parties shall co-operate in this regard.

Investigator Name: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Signature: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Date: \_\_\_\_\_\_\_\_\_\_\_\_

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**Abbreviations and Definitions of Terms**

ACE Angiotensin Converting Enzyme

AE Adverse Event

ARB Angiotensin Receptor Blockers

BP Blood Pressure

BTT Bridge to Transplant

CAD Coronary Artery Disease

CPB Cardio-pulmonary bypass

CRF Case Report Form

CVP Central Venous Pressure

DT Destination Therapy

ECG Electrocardiogram

EDV End Diastolic Volume

EDD End Diastolic Diameter

EF Ejection Fraction

eGFR estimated Glomerular Filtration Rate

ESD End Systolic Diameter

ESV End Systolic Volume

GCP Good Clinical Practice

GP General Practitioner

ICD Implantable Cardioverter Defibrillators

IRB Institutional Review Board

IVS Intraventricular Septum

KCCQ Kansas City Cardiomyopathy Questionnaire

LC/MS/MS Liquid Chromatography-Tandem Mass Spectrometry

LHF Left Heart Failure

LVAD Left Ventricular Assist Device

MAP Mean Arterial Pressure

NT proBNP N-terminal Prohormone of Brain Natriuretic Peptide

NYHA New York Heart Association classification

PAP Pulmonary Artery Pressure

PCWP Pulmonary Capillary Wedge Pressure

PICF Patient Informed Consent Form

PVR Pulmonary Vascular Resistance

RV Right Ventricle

RVF Right Ventricular Failure

RVSP Right ventricular Systolic Pressure

SAE Serious Adverse Event

SIRS Systemic Inflammatory Response Syndrome

TAPSE Tricuspid Annular Plane Systolic Excursion

TEAE Treatment Emergent Adverse Event

TR Tricuspid Regurgitation

VAD Ventricular Assist Device

VT Ventricular Tachycardia

VF Ventricular Fibrillation

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1. Synopsis

|  |  |
| --- | --- |
| Study Title: | Investigator Led Study of Intravenous Milrinone in Heart Failure with Preserved Ejection Fraction (HFpEF). |
| Protocol Number: | **MilHFpEF-IV-02** |
| Development Phase: | Phase Ib |
| Indication: | Efficacy study in HFpEF patients |
| Study Drugs: | IV milrinone |
| No. Subjects: | 8 patients (6 treated and 2 placebo) |
| Study Duration: | Single day procedure  Entire study estimated to be completed in 6 months |
| Objectives of the Study: | To investigate the effects of intravenous milrinone on rest and exercise hemodynamics in HFPEF patients. |
| Endpoints: | Exploratory endpoints:  Changes compared to baseline (at rest, 20 W and peak supine exercise) in:   * Pulmonary capillary wedge pressure * Pulmonary artery pressures (mean, systolic, diastolic and pulse pressure) and derived parameters including pulmonary arterial compliance and elastance * Cardiac output (thermodilution) * Systemic blood pressure (measured non-invasively) * Peripheral vascular resistance * Heart rate   Safety Endpoint:   * All adverse event (AE) recording and assessments. |
| Study Design: | Randomized, double blind, placebo controlled |
| Inclusion and Exclusion Criteria | Inclusion Criteria:   1. Males and females aged 18-85. 2. Symptoms of heart failure (NYHA class III or ambulatory class IV). 3. Left Ventricular Ejection Fraction (LVEF) ≥50%. 4. Heart Failure hospitalization within 12 months or NT-proBNP >125 pg/mL. 5. Evidence of prior diagnosis of HFpEF, confirmed via:  * Echocardiographic parameters (one or more of the following) observed//recorded in previous 6 months:   + septal E/e’ ≥ 13 (a measure of LV filling pressure) or   + left atrial volume index > 34ml/m2 or   + LV mass index ≥ 115 g/m2 (male) or ≥ 95 g/m2 (female).   or   * Hemodynamic exercise test within 12 months.  1. Stable medical heart failure therapy including diuretics for 2 weeks. 2. Able to give written informed consent and agree to adhere to all protocol requirements. 3. Potassium between 4 – 5.5mmol/L   Exclusion Criteria:   1. Myocardial infarction or acute coronary syndromes within 90 days. 2. Hypotension (systolic BP <90 mmHg) at Screening or Baseline 3. Severe Hypertension (systolic BP >180 mmHg) at Screening or Baseline 4. Poorly controlled atrial fibrillation (ventricular rate>120bpm). 5. History of significant ventricular arrhythmia in the past year 6. Significant renal impairment (eGFR <30 ml/min/1.73 m2) 7. Severe physical limitation defined by inability to complete a minimum exercise tolerance time of 120 seconds on two treadmill tests within 2 weeks of enrollment 8. Restrictive or infiltrative cardiomyopathy. 9. Pregnancy 10. History of allergic reaction to milrinone or any excipients in the study drug. 11. Participation in another clinical trial |
| Study Overview: | This is a phase 1b, exploratory study to evaluate the effect of IV milrinone on exercise hemodynamics.  This is a double blinded, placebo-controlled investigator led trial. The study cohort will comprise of 8 patients (6 active, 2 placebo). Subjects who are successfully screened will be enrolled into trial.  After baseline evaluation on day 1, subjects will be randomly allocated. After the baseline rest and exercise haemodynamic evaluation, subjects will be randomised to receive either active (milrinone) or placebo (saline) infusion.  At the conclusion of the infusion, rest and exercise measures will be repeated. Exercise will be conducted at individual matched workloads and durations1. The primary objective was to compare the between-group changes in exercise hemodynamics after administration of placebo versus milrinone. Parameters to be evaluated are described in the prior sections. |
| Statistical Analyses: | Changes invariables described above will be compared using a paired t-test |

Table 1: Schedule of Procedures

|  |  |  |
| --- | --- | --- |
| Visit | Screening | Study day2 |
| Timing/window | Day -28 to 1 | Day 1 |
| Informed consent | X |  |
| Inclusion/Exclusion criteria | X |  |
| Demographics | X |  |
| Medical/medication history | X | X |
| physical exam | X | X |
| Vital signs | X | X |
| NYHA Class | X | X |
| Haematology | X |  |
| Biochemistry, EUC, LFT | X | X |
| BNP and NT proBNP | X | X |
| Troponin | X | X |
| 12 Lead ECG | X | X |
| Rest and Exercise Hemodynamic evaluation |  | X |
| Plasma milrinone levels1 |  | X |
| Adverse event monitoring |  | X |

1 To be taken at the end of infusion, and at the end of exercise test. 2 plasma levels will need to be taken

2 A focused cardiovascular exam will be conducted at the study visit by the PI or a designated specialist heart failure/LVAD cardiologist at day 1.

1. Introduction
   1. Heart Failure with Preserved Ejection Fraction

Heart failure (HF) is one of the most common and most disabling forms of cardiovascular disease. Moreover, HF is particularly prevalent in older individuals, affecting up to 10% of the population over 75 years2. From a clinical and epidemiologic point of view it is important to note that the diagnosis of HF is based initially upon the presence of well-recognized symptoms and signs, for example as used in the Framingham criteria3. Subsequent to the clinical diagnosis, the application of diagnostic investigations such as echocardiography can then be used to identify the pathophysiology of the clinical phenotype together with the provision of prognostic and therapeutic information. Amongst the echocardiographic parameters that are applied to the assessment of ventricular function, the ejection fraction remains in common use despite numerous limitations including its sensitivity to loading conditions and technical issues with endocardial border definition and geometric assumptions4, 5. This stated, we now appreciate that approximately 50% of HF patients both in community studies and in registries of patents admitted with acutely decompensated HF have a normal or near normal ejection fraction, termed HF with preserved ejection fraction (HFPEF)6, 7.

The clinical profile of patients with HFPEF differs substantially to those with reduced ejection fraction HF (HFREF). Patients are older, more likely to be female, more obese, and have different contributing risk factors. Coronary artery disease is less common, whilst rates of hypertension, diabetes, and atrial fibrillation are greater8. African Americans may develop HFPEF at a younger age9. Consistent with the increased age of the population, the rate of non-cardiac comorbidities is also higher10, including chronic lung disease, anaemia, chronic kidney disease, and malignancy. These co-morbidities are responsible for a significant proportion of the morbidity and mortality associated with HFPEF, although the majority of limitation to exercise intolerance is cardiac11. Renal dysfunction, defined as an abnormal glomerular filtration rate (GFR) or as microalbuminuria, has been shown to independently predict changes in left ventricular (LV) geometry, and has been implicated in the pathogenesis of HFPEF12. Diabetic HFPEF patients have a significantly higher rate of hospitalisation and a reduced exercise capacity13. Atrial fibrillation is common in this group, making up of a quarter of the population, and is associated with the same risk of stroke as those with a reduced ejection fraction13.

* 1. HFpEF Management

Similar to patients with HFREF, the objectives of HF treatment in general are to improve quality of life, reduce hospitalisation, to reduce mortality and given the linkage between cardiac structure and the clinical phenotype to reverse cardiac remodelling. To date, clinical trials in HFPEF have largely been disappointing perhaps reflecting variability in trial design14-19, relatively limited study duration in comparison to the likely duration required for the development of HFPEF and the possibility that the disease mechanisms are not yet fully understood. The main principles of the management of HFPEF are to maintain strict control of blood pressure, relieve congestion, prevent ischemia, treat co-morbid conditions, and maintain atrial function through rate or rhythm control.

As in patients with HFREF, the appropriate use of diuretics in the setting of volume overload in individuals with HFPEF is an important key to symptom relief. Avoidance of over-diuresis is important given the frequent co-existence of renal impairment together with the fact that HFPEF patients typically have a reduced stroke-volume and may be particularly sensitive to excessive reductions in pre-load. Building upon the very strong evidence base for ACE inhibitors and ARBs in HFREF, several large scale trials of these agents were conducted in HFPEF14, 20, 21 using drugs including perindopril, irbesartan and candesartan. Whilst trials failed in their primary endpoints, there was evidence of a modest reduction in hospitalisation for both ARBs and ACE inhibitors.

Although detailed studies of the activity of the sympathetic nervous system in HFPEF have not been conducted, it has been postulated that beta blockers could be useful in HFPEF by extending diastolic filling time and reducing ischemia. Some patients with HFPEF have evidence of chronotropic incompetence22, and trials assessing both nebivolol23 and carvedilol24 in this respect have been negative. Short term use of ivabradine has been shown to improve exercise capacity25, and larger studies are under way. In patients with atrial fibrillation, control of the ventricular rate is paramount8.

Based upon the hypothesis that activation of the renin-angiotensin-aldosterone system is important in the pathogenesis of HFPEF, studies have been conducted into the utility of spironolactone. In the Aldosterone Receptor Blockade in Diastolic Heart Failure (Aldo-DHF) study26 there was evidence of improved diastolic function however with no other signal of benefit. In the larger TOPCAT outcome study, spironolactone treatment was not associated with improved survival, although there was evidence of a modest reduction in HF hospitalisation16. Importantly in both studies blood pressure was also lowered.

* 1. Rationale for Performing the Study:

Kaye previously tested the hypothesis that milrinone may be beneficial in HFpEF30 .This concept was based on the properties of milrinone, a phosphodiesterase type III inhibitor. The drug exhibits several pharmacological actions that may be favorable in HFPEF. These include beneficial effects on left ventricular diastolic function, pulmonary vasodilation and systemic vasodilation when investigated in the setting of reduced ventricular function. Milrinone exhibits positive inotropic actions which may also potentially offer some value in HFPEF, given it has been demonstrated that some aspects of LV systolic function are reduced in HFPEF. In the study performed by Kaye, the effects of a single dose of milrinone, 50ug/kg, were investigated on rest and exercise hemodynamics. The study showed the drug significantly reduced rest and exercise pulmonary capillary wedge pressures30 .Within this context, this study aims to examine the effects a lowdoseof intra-venous (iv) milrinone to determine the concentration/dose vs hemodynamic profile.

1. Study Objectives
   1. Objectives

The primary objective of the study is to:

* To determine the effectiveness of a low dose of iv milrinone on exercise hemodynamics in HFpEF patients.

1. Study Description

This is a phase 1b, randomized placebo controlled Investigator led study to assess the dose response of a low dose (25ug/kg) of iv milrinone or placebo in 8 subjects with HFpEF.

After Screening, eligible subjects will return for the study day during which they will undergo a right heart catheterization study while receiving a specified dose of iv milrinone or placebo.

1. Study Population

The study population will include patients with heart failure with preserved ejection fraction (HFpEF), recruited from stable outpatients.

* 1. Selection Criteria

### Inclusion Criteria

Patients are enrolled only if they met the following criteria.

1. Males and females aged 18-85.
2. Symptoms of heart failure (NYHA class III or ambulatory class IV).
3. Left Ventricular Ejection Fraction (LVEF) ≥50%.
4. Heart Failure hospitalization within 12 months or NT-proBNP >125 pg/mL.
5. Evidence of prior diagnosis of HFpEF, confirmed via:
   * Echocardiographic parameters (one or more of the following) observed//recorded in previous 6 months:
     + septal E/e’ ≥ 13 (a measure of LV filling pressure) or
     + left atrial volume index > 34ml/m2 or
     + LV mass index ≥ 115 g/m2 (male) or ≥ 95 g/m2 (female).

*or*

* + Hemodynamic exercise test within 6 months.

1. Stable medical heart failure therapy including diuretics for 2 weeks.
2. Able to give written informed consent and agree to adhere to all protocol requirements.
3. Potassium between 4 – 5.5 mmol/L

### Exclusion Criteria:

1. Myocardial infarction or acute coronary syndromes within 90 days.
2. Hypotension (systolic BP <90 mmHg) at Screening or Baseline
3. Severe Hypertension (systolic BP >180 mmHg) at Screening or Baseline
4. Poorly controlled atrial fibrillation (ventricular rate>120bpm).
5. History of significant ventricular arrhythmia in the past year
6. Significant renal impairment (eGFR <30 ml/min/1.73 m2)
7. Severe physical limitation defined by inability to complete a minimum exercise tolerance time of 120 seconds on two treadmill tests within 2 weeks of enrollment
8. Restrictive or infiltrative cardiomyopathy.
9. Pregnancy
10. History of allergic reaction to milrinone or any excipients in the study drug.
11. Participation in another clinical trial
    1. Prior and Concomitant Therapies Medications

All concomitant therapies taken within 7 days of screening up until the closeout visit will be captured in the source documents and CRF. All patients are required to be on optimal medical therapy for heart failure as determined by their managing cardiologist.

The following medications are prohibited from 7 days prior to screening through to the end of treatment:

Intravenous inotropes (milrinone, dobutamine, epinephrine, levosimendan), cilostazol

1. Investigational Product
   1. Description

The product investigated is the approved product, iv milrinone (Primacor®) .

* 1. Packaging and Labeling

The study drug is provided in glass ampoules for dilution in 0.9% NaCl. Ampoules are labeled according to relevant guidelines and legislation.

* 1. Storage, Dispensing and Reconciliation of Study Drug

Milrinone will be dispensed blinded via The Alfred Clinical Trials Pharmacy. Randomisation log/envelope to be kept by pharmacy.

Investigational product should be stored at 25oC or below. Do not freeze. Temperature excursions up to 30oC are permitted.

The Principal Investigator is responsible for drug product accountability, reconciliation, and record maintenance. The Principal Investigator or designated site staff must maintain drug product accountability records throughout the course of the study including records for the amount of investigational product received, the identification of the subject for whom the drug was dispensed, the date(s) and the quantity of the drug dispensed and any amount returned.

1. Study Endpoints
   1. Exploratory

Changes compared to baseline in:

* Pulmonary capillary wedge pressure
* Pulmonary artery pressures (mean, systolic, diastolic and pulse pressure) and derived parameters including pulmonary arterial compliance and elastance
* Total (thermodilution) cardiac output
* Systemic blood pressure (measured non-invasively)
* Peripheral vascular resistance
* Blood pressure and heart rate
* Cardiac index.
* Blood pressure (mean and systolic, where appropriate)
* Plasma milrinone levels
  1. Primary (safety)
* All adverse event (AE) recording and assessments.

1. Study Procedures

Table 2 outlines the study procedures to be completed.

Table 2: Study Procedures.

|  |  |  |
| --- | --- | --- |
| Visit | Pre-screening | Study day2 |
| Timing/window | Day -28 to 1 | Day 1 |
| Informed consent | X |  |
| Inclusion/Exclusion criteria |  |  |
| Demographics |  | X |
| Medical/medication history | X | X |
| physical exam | X | X |
| Vital signs | X | X |
| NYHA Class | X | X |
| Haematology | X |  |
| Biochemistry, EUC, LFT | X | X |
| BNP and NT proBNP | X | X |
| Troponin | X | X |
| 12 Lead ECG | X | X |
| Rest and Exercise Hemodynamic evaluation |  | X |
| Plasma milrinone levels |  | X |
| Adverse event monitoring |  | X |
| Concomitant medications | X | X |

1 To be taken at the end of infusion, and at the end of exercise test. 2 plasma levels will need to be taken

2 A focused cardiovascular exam will be conducted at the study visit by the PI or a designated specialist heart failure/LVAD cardiologist at day 1.

* 1. Exploratory Endpoints
* Hemodynamic Evaluation: Subjects will undergo right heart catheterisation via the cubital vein or internal jugular vein according to local clinical practice at baseline and follow up visits. Right atrial, right ventricular and pulmonary artery and wedge pressures will be measured at gentle held expiration. Thermodilution cardiac output measurement will be performed in triplicate.
  + Following baseline measures, subjects will supine perform symptom-limited supine cycling at incremental levels of 20 Watts for 3 minutes (exercise will not be performed if the resting RHC unexpectedly demonstrates severe pulmonary hypertension PA systolic>60mmHg). The test will be stopped when the patient experiences limiting dyspnoea or other limiting symptoms. Measures will be obtained at rest, 20W and peak exercise.
  + Following initial rest and exercise evaluation, patients will be randomly allocated to receive either a standard loading dose of milrinone (25 ug/kg) over 10 min or placebo. Neither the patient nor the investigator will know which group the subject has been allocated to.
  + Rest and exercise hemodynamic (as above) will be repeated after a further 10 minutes.
* At the designated time point (after 20 minute infusion), blood will be drawn (2 samples) for the measurement of plasma milrinone levels. Blood samples will be collected and stored according to the Study Reference Manual. CRD-102 levels (ng/mL) will be determined using liquid chromatography- tandem mass spectrometry (LC/MS/MS) by CPR Pharma Services Pty Ltd, Adelaide, Australia.
  1. Safety Endpoints

Safety will be assessed by recording of AEs, vital signs, laboratory parameters, and physical/cardiovascular examinations.

* Each subject will undergo a complete medical history (including weight measurement) and physical exam prior to randomization to assess their clinical status and to confirm eligibility for study participation. Physical examinations during the study will include height (at Screening only) and weight, and assessment of skin, head, neck, lymphatic, eyes, ears, nose and throat, abdomen, and respiratory, cardiovascular/peripheral vascular, endocrine, central nervous, genitourinary and musculoskeletal systems as appropriate to determine general condition. New or worsening clinically significant abnormalities will be reported as an AE. Post Screening, a symptom-directed PE will be conducted if required, based on prior findings and symptoms.
* A focused cardiovascular exam will be conducted at the study visit by the PI or a designated specialist heart failure cardiologist.
* Subjects will undergo a 12-lead ecg at the study visit.
* Subjects will be questioned and monitored throughout the study with regard to any AEs they may have experienced. See Section 9 for further details on recording AEs.
* Blood samples will be taken for safety assessments. The following specific tests will be performed at the site’s local pathology laboratory:

Haematology: Haemoglobin, haematocrit, red blood cell (RBC) count, white blood cell (WBC) count with differential, and platelet count.

Serum Chemistry: Sodium, potassium, urea, gamma glutamyl transferase (GGT), aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), total bilirubin, lactate dehydrogenase (LDH), and creatinine (calculated creatinine clearance using the Cockcroft and Gault formula).

* Vital signs will be measured after the subject has been supine for 10 minutes and will include blood pressure (BP) on the same arm (if possible) throughout study, pulse rate, respiratory rate and temperature. Blood pressure will be measured in the semi-recumbent position, according to the preferred method by the Principal Investigator, optimized for each patient (ie Doppler, oximetry or automated oscillometry as appropriate). Blood pressure will be notated at the visit as mean or systolic according to the audible profile. Heart rate will be recorded over a 30 second period.
  1. Medical Monitoring

The Principal Investigator will designate a Medical Monitor for safety and clinical reporting. This Medical Monitor will review safety endpoints and subject data, and answer queries from both Investigators and study personnel. The Medical Monitor and the Principal Investigator will review data periodically from a 5 subject block. The Medical Monitor will provide regulatory oversight from a clinical perspective.

* 1. Study Visits

The study will be conducted over 1-day time period with 1 screening visit and 1 day-one visit. (Both screening and study visits can be performed on the same day if required). The study schedule is outlined in Table 1.

### Informed Consent Process

The Investigator must provide adequate information regarding the study conduct and obtain written informed consent from the subject before any tests or investigations outlined in the study protocol are carried out. Patients will be provided with a copy of the Participant Information and Consent Form (PICF) to read and discuss with family members, friends or family doctor. Any questions or concerns will be answered by the investigator administering the consent. Patients will be invited to participate if they demonstrate an understanding of what the study involves, the risks and the procedures involved. The PICF must be personally signed and dated by both the Investigator obtaining consent and the subject. The patient will be given a copy of the signed PICF. The original will be retained by the site.

### Screening Visit (Day -28 to Day 1)

The purpose of the Screening visit is to confirm subject eligibility against inclusion and exclusion criteria. Screening assessments may be performed on different days within the Screening period, if required.

Once written informed consent has been obtained, the following visit assessments and procedures will be performed;

* Review eligibility criteria.
* Record subject demographic data.
* Review and record medical and medication history, and current conditions and medications.
* Physical examination including height and weight (see Section 8.1).
* Vital signs (see Section 8.1).
* 12 lead ECG
* Blood sample for BNP and NT proBNP tests
* Safety laboratory tests including haematology and biochemistry

### Re-Screens

One repeat test of each individual screening assessment (e.g., laboratory tests, ECG) is allowed, within the screening period.

### Study Day (Day 1)

Subjects will return to the site for hemodynamic evaluation.

* Review eligibility criteria.
* Review and record any new medical conditions since the Screening Visit as medical history
* Review and record any changes to medications
* Cardiovascular examination (see Section 8.1).
* Vital signs (see Section 8.1).
* 12 lead ecg
* Record subject’s NYHA Class
* Safety laboratory tests including haematology and biochemistry (see Section 8.1).
* Concomitant medication review.
* Hemodynamic exercise evaluation
  1. Early termination visit

Not applicable.

1. Adverse Events
   1. Definitions

An adverse event is any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment.  An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

* 1. Monitoring

Adverse events will be collected and recorded in the CRF for subjects.

Throughout the study, reported and observed AEs will be documented in the medical records and the CRF, along with their intensity, whether or not considered treatment-related. This will include any new signs, symptoms, injury or illness, including increased severity or frequency of previously existing signs, symptoms, injury, or illness.

Conditions existing prior to screening will be recorded as part of the subject’s medical history.

The investigator will be responsible for assessing the relationship of AEs to the study medication; relationship will be classified as not related, unlikely related, probably related, or definitely related.

The Investigator will follow-up on all AEs until they resolve, become stable, or until they can be explained by another known cause(s) (i.e., concurrent condition or medication) and clinical judgment indicates that further evaluation is not warranted.  All findings relevant to the final outcome of an AE will be reported in the subject’s medical record.

### Intensity of Adverse Events

The intensity (or severity) of AEs is characterized as mild, moderate, or severe:

**Mild:** Causes no limitation of usual activities

**Moderate:** Causes some limitation of usual activities

**Severe:** Prevents or severely limits usual activities

### Relationship to Study Medication

The degree of “relatedness” of the AE to IV milrinone will be assigned by the PI using the following scale:

**Not related:** AE for which there is evidence of another explanation, e.g. the adverse event is obviously explained by the subject’s disease(s), is in accordance with the known effect of a concomitant medication or has occurred prior to first administration of IV milrinone.

**Unlikely related:** AE with a time to IV milrinone administration that makes a relationship improbable (but not impossible), and disease or other drugs provide plausible explanations

**Probably related:** AE with reasonable time relationship to IV milrinone administration that is unlikely to be attributed to disease or other drugs. Response to IV milrinone withdrawal is clinically reasonable. Rechallenge is not required.

**Definitely related:** AE with plausible time relationship to IV milrinone administration which cannot be explained by disease or other drugs. Response to IV Milrinone withdrawal is plausible (pharmacologically, pathologically), and event is definitive pharmacologically or phenomenologically (i.e. an objective and specific medical disorder or a recognised pharmacological phenomenon). Rechallenge, if performed/necessary, is satisfactory.

* 1. Serious Adverse Events

A SAE is defined as an AE that:

* Results in death
* Is immediately life-threatening (there is an immediate risk of death from the AE as it occurred; this does not include an AE that had it occurred in a more serious form may have caused death)
* Results in or prolongs an in-patient hospitalization (Note: Hospitalisation is defined as in-patient admission or care regardless of duration.)

Out-patient treatment in an emergency room is not in itself an SAE, although the reasons for it may be (e.g. bronchospasm, laryngeal oedema). Elective surgery, hospitalisation for social reasons (with no causal AE), or hospital admissions and/or surgical operations planned before or during this study are not considered AEs if the illness or disease existed before the subject was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.)

* Results in persistent or significant disability (permanent or substantial disruption of one’s ability to conduct normal life functions)
* Is a congenital anomaly/birth defect (in offspring of a subject using the study medication regardless of time to diagnosis)
* Is considered an important medical event
  + Important medical events are defined as events that, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes defining an SAE. Examples of important medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in in-patient hospitalization, or the development of drug dependency or drug abuse.

### Reporting of Serious Adverse Events

Investigators and other site personnel must report SAEs to The Alfred Hospital HREC or designee within 24 hours of becoming aware of the SAE, regardless of causality.

Follow-up information on SAEs must also be reported by the investigational site within the same time frame. If a non-serious AE becomes serious, this and other relevant follow-up information must also be provided within 24 hours.

* 1. Clinical Laboratory Abnormalities and Other Abnormal Assessments as AEs and SAEs

Abnormal laboratory findings (e.g. clinical chemistry, hematologys) or other abnormal assessments (e.g. vital signs) that are judged by the investigator as clinically significant will be recorded as AEs or SAEs if they meet the definition of an AE, as defined in Section 7.2 or SAE as defined in Section 7.3. Clinically significant abnormal laboratory findings or other abnormal assessments that are detected during the study or are present at baseline and significantly worsen following the start of the study will be reported as AEs or SAEs. However, clinically significant abnormal laboratory findings or other abnormal assessments that are associated with a disease reported in the medical history, unless judged by the investigator as more severe than expected for the subject’s condition, or that are present or detected at the start of the study and do not worsen, will not be reported as AEs or SAEs.

1. Statistical Considerations
   1. Sample size

8 patients at the dose level 25ug/kg/hr will be included in the trial. This will comprise of 6 patients receiving active (IV milrinone), and 2 patients being assigned to receiving placebo. Up to a maximum of 8 patients may be studied.

### Safety Evaluations

The safety measurements evaluated will be clinical assessment of vital signs, physical examinations and cardiovascular examinations, MACCE, adverse (AE) and serious adverse event (SAE) monitoring throughout the protocol. In addition, laboratory safety assessments (haematology and biochemistry) will be conducted. All subjects who receive any amount of the drug product will be included in the Safety Population.

### Exploratory Evaluations

The exploratory evaluations of the will be study will examine changes compared to baseline in:

* Pulmonary capillary wedge pressure
* Pulmonary artery pressures (mean, systolic, diastolic and pulse pressure) and derived parameters including pulmonary arterial compliance and elastance
* Cardiac output (thermodilution)
* Systemic blood pressure (measured non-invasively)
* Peripheral vascular resistance
* Heart rate
* Blood pressure (mean and systolic, where appropriate)

1. Data Management

A Case Report Form (CRF) will be completed by authorised study site personal designated by the investigator for each study subject summarising all study data. Subjects will only be referred to in the CRF by their subject number in order to retain subject confidentiality.

The CRFs should always reflect the latest observations on the subjects participating in the trial; therefore, the CRFs are to be completed as soon as possible after the subject’s visit. The Investigator must verify that all data entries in the CRFs are accurate and correct. If some assessments are not done, or if certain information is not available or not applicable or unknown, this should be indicated in the CRF. The Investigator will be required to sign off on the clinical data.

* 1. Source Data and Retention of Records

Source documents are original documents, data, and records from which the subject’s CRF data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, and correspondence. In this study, CRFs may not be used as source documents.

The Investigator is responsible for maintaining source documents. Data from this study may be shared with Cardiora Pty Ltd, a company that has interest in developing another form of milrinone for HFPEF subject to additional ethics review and approval at the time of sharing.

1. Estimated Duration of the Study

It is anticipated that this study will be conducted over a 6- month duration.

* 1. Participant Information and Informed Consent

Prior to the commencement of any study specific procedure, participants are to be informed of the study, invited to participate, handed a written participant information sheet and consent form (PICF) and given the opportunity to discuss the study with family, friends, the participants General Practitioner (GP) and the study Principal Investigator (PI). The study participant will then be asked to sign the EC/IRB approved PICF, and a copy of the completed PICF given to the participant.

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