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STUDY DESIGN

# Safety and efficacy of up to 60 h of iv istaroxime in pre-cardiogenic shock patients: Design of the SEISMiC trial

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## Abstract

**Aims** Cardiogenic shock (CS) is linked to high morbidity and mortality rates, posing a challenge for clinicians. Interventions to improve tissue perfusion and blood pressure are crucial to prevent further deterioration. Unfortunately, current inotropes, which act through adrenergic receptor stimulation, are associated with malignant arrhythmias and poorer outcomes. Due to its unique mechanism of action, istaroxime should improve haemodynamics without adrenergic overactivation. The SEISMiC study is designed to examine the safety and efficacy (haemodynamic effect) of istaroxime administrated in pre-CS patients.

**Methods and Results** The SEISMiC study is a multinational, multicentre, randomized, double-blind, placebo-controlled safety and efficacy study with two parts (A and B). The study enrols patients hospitalized for decompensated heart failure (pre-CS, not related to myocardial ischaemia) with persistent hypotension [systolic blood pressure (SBP) 70–100 mmHg for at least 2 h] and clinically confirmed congestion, NT-proBNP $\geq$1400 pg/mL, and LVEF$\leq$40%. Subjects must not have taken intravenous (iv) vasopressors, inotropes or digoxin in the past 6 h. Eligible patients are randomized to receive IV infusion of istaroxime (different doses and regimens in Parts A and B) or placebo for up to 60 h. Central haemodynamics, ECG Holter monitoring, cardiac ultrasound and biomarkers are recorded at predefined time points during the trial. The study's primary efficacy endpoint is the SBP area under the curve from baseline curve from baseline to 6 and 24 h in the combined SEISMiC Parts A and B population. Key secondary efficacy endpoints include haemodynamic, laboratory and clinical measures in SEISMiC B alone in the combined SEISMiC A and B studies.

**Conclusions** The study results will contribute to our understanding of the role of istaroxime in pre-CS patients and potentially provide insight into the drug's haemodynamic effects and safety in this population.

**Keywords** cardiac calcitrope; cardiogenic shock; central haemodynamics; inotrope; istaroxime; pre-cardiogenic shock

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## Introduction

Pre-cardiogenic shock and cardiogenic shock (CS) continues to be associated with high rates of morbidity and mortality, presenting a therapeutic challenge for clinicians and necessitating interventions to prevent deterioration to overt CS that is related to the worst outcomes.[1–5] Interventions that can improve tissue perfusion and blood pressure and are well tolerated seem particularly necessary, as hypoperfusion/hypotension are the major causes of end-organ injury and poor outcomes.[6,7] Current vasopressors and inotropes, acting through adrenergic receptor stimulation, are associated with tachycardia, malignant arrhythmias and, in many studies, poorer outcomes.[3,8–12]

Istaroxime is a derivative of androstenedione, and it is not chemically related to cardiac glycosides.[13] It works through dual mechanisms of action: (1) by inhibiting the Na+/K+-ATPase activity, causing an increase in intracellular calcium, which enhances cardiomyocyte contractility (inotropy); and (2) by activating the sarcoplasmic reticulum calcium ATPase isoform 2a (SERCA2a) through modulating SERCA–phospholamban interaction.[14] This promotes sarcoplasmic reticulum calcium reuptake, thus improving contraction, relaxation (lusitropy) and contractility.[10,15] Due to its unique mechanism of action, istaroxime should improve central haemodynamics (an increase in cardiac output and systemic blood pressure with a decrease in pulmonary capillary wedge pressure) without a rise in heart rate and adrenergic overactivation.[16–19]

The SEISMiC study was designed to assess the ability of istaroxime to increase systolic blood pressure (SBP) in patients with Stage B Society for Cardiovascular Angiography and Interventions (SCAI) CS[20,21] due to acute heart failure (HF) (AHF) without acute coronary syndrome.[22] Results for the initial part of the study ('Part A') have already been published.[23] Sixty patients were randomized 1:1 to placebo or istaroxime administered at the doses of 1.0 or 1.5 μg/kg/min over 24 h. A statistically significant difference was found between treatment groups in the area under the curve representing the change from baseline in SBP (SBP AUC) to 6 h (53.1 vs. 30.9 mmHg·h in the istaroxime and placebo groups, respectively; $P = 0.017$).[23] The benefits of istaroxime appeared to be reached at dosages less than 1.5 μg/kg/min (i.e., 1.0 μg/kg/min).[24] Istaroxime has a short half-life (<1 h) and is given by continuous infusion. A terminal metabolite of istaroxime has a longer half-life, approximately 14 h, and is a selective SERCA2a activator. Longer dosing may provide the potential to assess isolated SERCA2a activation in humans. Therefore, we designed of the extension of the SEISMiC study ('Part B') in which the dose response to istaroxime was further explored in patients randomized to a 60 h infusion of one of two istaroxime regimens or placebo.

## Study design

SEISMiC is a pilot, multinational, multicentre, randomized, double-blind, placebo-controlled safety and efficacy study. Patients were sequentially enrolled under a single protocol in two parts (Parts A and B), with different dosing regimens and a slightly wider screening SBP allowed for inclusion in Part B of the study. In Part B, male or female subjects aged 18–85 years hospitalized for acute decompensated HF (ADHF) with persistent hypotension (SBP 70–100 mmHg for 2 h) and heart rate 75–150 beats/min, congestion on chest X-ray or lung ultrasound, NT-proBNP ≥1400 pg/mL and LVEF ≤ 40% are eligible. Subjects must not have taken intravenous (iv) vasopressors, inotropes or digoxin in the past 6 h. The detailed list of inclusion/exclusion criteria is given in *Table* 1. Sites from North America, South America and Europe are participating in this study. Thirty patients have been enrolled in Part B.

The study is being conducted in accordance with the Declaration of Helsinki. Approvals from appropriate regulatory authorities and institutional review boards or ethics committees were obtained. Patients provided their written, informed consent to participate. The trial is registered on clinicaltrials.gov (NCT04325035).

### Study intervention

Patients were to be randomized within 36 h of hospital admission and a maximum of 24 h following informed consent. In Part B, patients were randomized 1:1:1 within the study site to a 60 h continuous infusion of either placebo or one of two istaroxime dosing regimens: (1) 1.0 μg/kg/min for 6 h, 0.5 μg/kg/min for 42 h, followed by 0.25 μg/kg/min for 12 h or (2) 0.5 μg/kg/min for 48 h followed by placebo for 12 h (*Figure* 1). Istaroxime and a matching placebo (lactose) were supplied as lyophilized powder in glass vials in blinded medication kits and reconstituted into infusion bags by local study staff in saline. A central statistician prepared the randomization scheme and loaded it for access by authorized site staff to randomize individual patients through a central interactive response technology (IRT) system. In case of an adverse event, the investigator could down-titrate, interrupt or discontinue the study drug, and re-initiate the study drug at the previous or reduced dose, but the study drug could not be administered after 60 h from initiation.

### Concomitant therapy

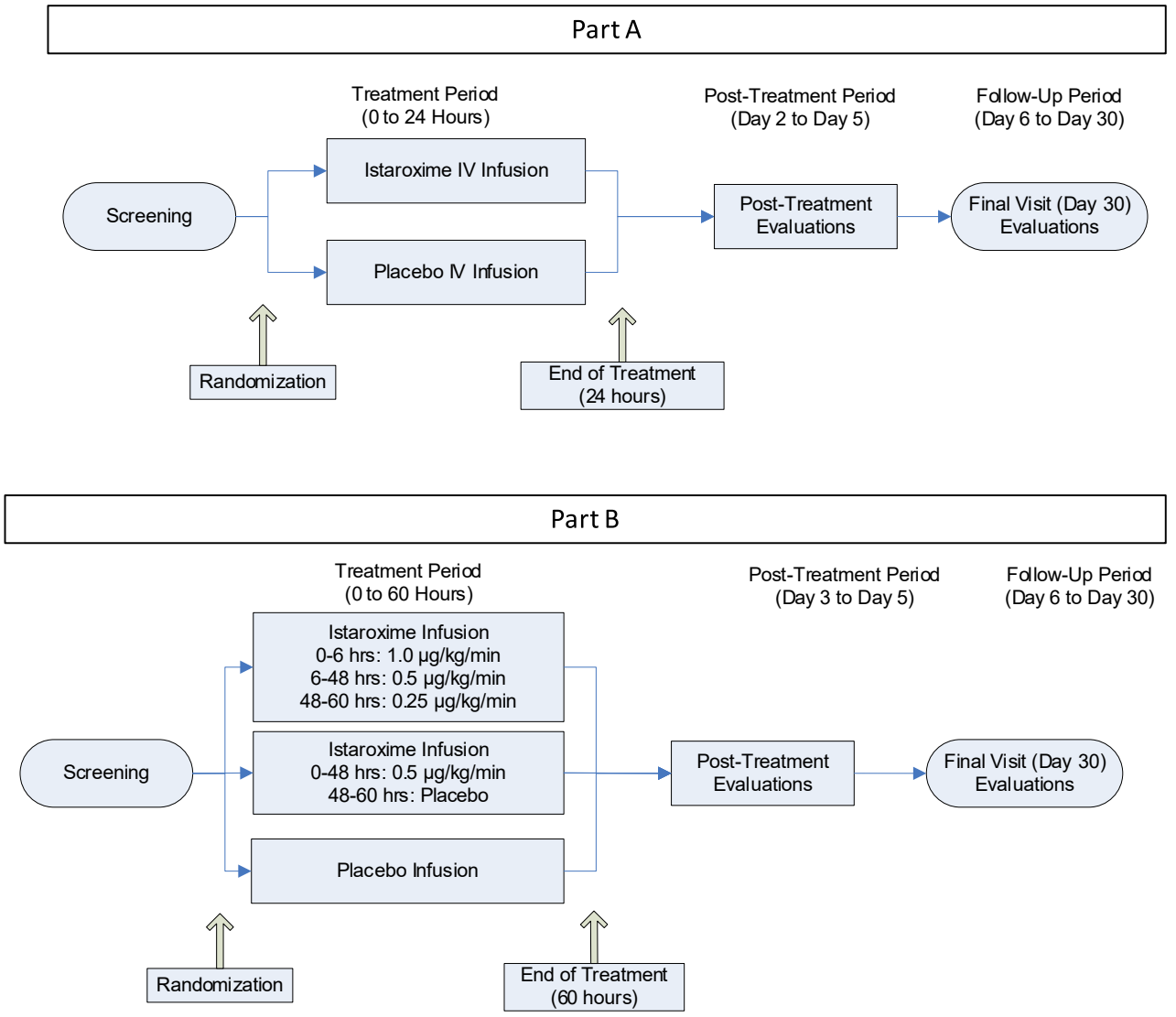
Patients who the investigator felt were likely to need rescue therapy (new treatment with iv-positive inotropic agents

**Table 1** Study inclusion and exclusion criteria.

| Inclusion criteria |
|---|
| All inclusion criteria must be met in order to be enrolled in this study:<br>1. Clinical presentation consistent with SCAI Stage B pre-cardiogenic shock caused by acute decompensation of chronic systolic heart failure (due to arterial hypertension, ischaemic heart disease or dilated cardiomyopathy), without evidence for an acute coronary syndrome.<br>2. Signed informed consent form (ICF);<br>3. Males and females, 18 to 85 years of age (inclusive);<br>4. An admission for an ADHF episode within 36 h prior to randomization, defined as follows:<br>a. Dyspnoea, at rest or with minimal exertion,<br>b. Congestion on chest x-ray or lung US with BNP $\geq$ 400 pg/mL or NT-proBNP $\geq$ 1400 pg/mL.<br>Elective admissions for medications tune up or procedures do not qualify as an ADHF admission.<br>5. History of left ventricular ejection fraction (LVEF) $\leq$ 40%;<br>6. Persistent hypotension defined as follows<br>a. SBP of 75 to 90 mmHg (Part A) or 70 to 100 mmHg (Part B) for $\geq$2 h prior to Screening;<br>b. Stable SBP, defined as no decrease in SBP by >7 mmHg on two separate measurements during the last 2 h prior to randomization;<br>7. Heart rate 75 to 150 bpm. If the subject is on a beta-blocker, the range is 60 to 150 bpm;<br>8. Echocardiogram during initial hospitalization confirming ejection fraction $\leq$40% and no evidence of other pathology to confound interpretation of cardiac physiology (e.g., pericardial effusion);<br>9. Subject is monitored by a PAC at the time of randomization (Part B only). |
| **Exclusion criteria** |
| Subjects meeting any exclusion criteria must not be enrolled in this study:<br>1. Cardiogenic shock of SCAI stage C or worse<br>2. Cardiogenic shock due to any other condition besides acute decompensation of chronic heart failure.<br>3. Any of the following in the past 60 days: acute coronary syndrome, coronary revascularization, MI, CABG or percutaneous coronary intervention;<br>4. Current (within 6 h of screening) or anticipated need for treatment with positive inotropic agents or vasopressors, renal support including ultrafiltration, or mechanical circulatory, ventilatory or renal support (intra-aortic balloon pump, endotracheal intubation, mechanical ventilation or any ventricular assist device);<br>5. Venous lactate >2 mmol/L;<br>6. History of heart transplant or UNOS priority 1a heart transplant listing;<br>7. Ongoing treatment with digoxin (if digoxin was stopped before signing the ICF and the digoxin plasma level is <0.5 ng/mL, the patient may be enrolled);<br>8. Severe renal impairment (eGFR < 30 mL/min, calculated by the MDRD formula);<br>9. Hypersensitivity to the study medication and its excipients (including known lactose hypersensitivity) or any related medication;<br>10. Stroke or TIA within 3 months;<br>11. Active coronary ischaemia;<br>12. Any significant valvular disease (including any moderate or severe valvular stenosis, moderate or severe aortic or pulmonary regurgitation or severe tricuspid or mitral regurgitation);<br>13. Primary hypertrophic or restrictive cardiomyopathy or systemic illness known to be associated with infiltrative heart disease;<br>14. Admission for AHF triggered primarily by a correctable aetiology such as significant arrhythmia (inclusive of atrial fibrillation as the main reason for admission), infection, severe anaemia, acute coronary syndrome, pulmonary embolism, exacerbation of COPD, planned admission for device implantation or over-diuresis as a cause of hypotension;<br>15. Pericardial constriction or active pericarditis;<br>16. Life-threatening ventricular arrhythmia, uncontrolled arrhythmia or implantable cardioverter defibrillator (ICD) shock or history of sudden death within 6 months;<br>17. Cardiac resynchronization therapy (CRT), ICD, ablation or pacemaker implantation (or planned implantation) within the past 3 months;<br>18. Sustained ventricular tachycardia in the last 3 months with no defibrillator;<br>19. Sustained hypotension (SBP < 70 mmHg) for at least 30 min from the time of arrival to the hospital;<br>20. Severe pulmonary disease or cor pulmonale or other causes of isolated right-sided HF or not related to left ventricular dysfunction;<br>21. Acute respiratory distress syndrome;<br>22. Suspected sepsis; fever >38°C or active infection requiring IV antimicrobial treatment;<br>23. Body weight <40 kg or $\geq$150 kg;<br>24. Laboratory exclusions:<br>a. Haemoglobin < 9 g/dL,<br>b. Platelet count < 100 000/μL,<br>c. Serum potassium > 5.3 mmol/L or <3.5 mmol/L;<br>25. A life expectancy <3 months based on the judgement of the investigator;<br>26. Uncontrolled thyroid disease;<br>27. Pregnant or breast feeding;<br>28. Ongoing drug or alcohol abuse;<br>29. Participation in another interventional study within the past 30 days. |

Abbreviations: ADHF, acute decompensated heart failure; AHF, acute heart failure; CABG, coronary artery bypass surgery; eGFR, estimated glomerular filtration rate; MI, myocardial infarction; NT-proBNP, N terminal pro brain natriuretic peptide; SBP, systolic blood pressure; SCAI, Society for Cardiovascular Angiography and Interventions; TIA, transient ischaemic attack; US, ultrasound.

**Figure 1** Study schema.




and vasopressors, renal support including ultrafiltration or mechanical ventilatory or circulatory support) within 6 h after randomization were not to be randomized (see *Table* 1). All attempts were to be made not to administer any treatments during the first 6 h after randomization, especially positive inotropic agents, mechanical ventilatory, circulatory support or renal support devices, including hemofiltration. The administration of such therapies through Day 5 is deemed a 'treatment failure'. Dosage of IV diuretics and/or oral HF medications should have remained stable for at least 2 h before the screening and during the entire 60 h treatment period after the start of infusion on Day 1, unless changes were required due to clinically relevant variations of the subject's condition.

## Study assessments and procedures

Study activities are detailed in *Table* 2. The trial contains a screening period (Days 0–1), a treatment period (Days 1–3: 0–60 h), a post-treatment period (Days 3–5) and a follow-up period (Days 6–30). Participants are followed up to Day 30, at which time the participant's overall health will be assessed, a physical examination will be performed and the details on hospitalizations and emergency/urgent care visits after the initial discharge will be recorded.

### *Vital signs and blood pressure*

At screening, vital signs (including blood pressure, weight, body temperature and oxygen saturation) and 12-lead ECG

**Table 2** Schedule of activities.

| Assessment/procedure | | | Screening period (Days 0–1) | Treatment period | | | Post-treatment period | | | | | | | | Follow-up period (Days 6–30) | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Part A: Day 1 (0–24 h) | | | Part A: Days 2–5 | | | | | | | | | |
| | | | | Part B: Days 1–3 (0–60 h) | | | | | | | | Part B: Days 3–5 | | | | |
| Hours relative to infusion start: | | | | Pre-dose | 0–12 | 13–23 | 24 | 30 | 36 | 48 | 60 | 72 | 84 | 96 | | |
| Informed consent | X | | | | | | | | | | | | | | | |
| Demog./medical hist./baseline char. | X | | | | | | | | | | | | | | | |
| Eligibility criteria | X | | | | | | | | | | | | | | | |
| Physical examination | X | | | | X | | | | X | | | X | | | X | X |
| Local laboratories | X | | | | X | | | | X | | | X | | | X | X |
| Serum pregnancy test[a] | X | | | | | | | | | | | | | | | X |
| Urinalysis | X | | | | | | | | | | | | | | | |
| EQ-5D[b] | | X | | | | | | | | | | | | | X | X |
| Echocardiography[c] | X | | X | | X | X[b] | X | | X | | X | | | | | |
| 12-Lead ECG | X | X | X[d] | | X | | | | X | | | X | | | X | X |
| Holter monitoring[e] | X | X[f] | ----> | ----> | -----> | -----> | -----> | | -----> | | -----> | -----\| | | | | |
| Invasive haemodynamics[g] | | X | X[h] | X[h] | X | X[b] | | | X[i] | | X | | | | | |
| Randomization | | X | | | | | | | | | | | | | | |
| Study Treatment[j] | | | X | X | X | X | X | | X | | X | | | | | |
| Pulse, SBP, and DBP[k] | X[l] | X | X[m] | X[m] | X[m] | X[m] | X[m] | | X[m] | | X[m] | X | | X | X | X |
| Oxygen saturation (pulse oximetry) | X | X | X[n] | X[n] | X | X | X | | X | | X | X | | | X | X |
| Weight | X | | | | X | | | | X | | | X | | | X | X |
| Body Temperature | X | X | | | X | | | | X | | | X | | | X | |
| Urine Collection | | | X[o] | -------\| | X[o] | -----> | ------\| | | X[o] | | -----> | -----\| | | | |
| Biomarkers/venous lactate (local) | X | X | X[d] | | X | | | | X | | | X | | | X | X |
| Sample collection for biomarkers | | X | X[d] | | X | | | | X | | | X | | | X | X |
| Sample collection for PK[p] | | X | X[p] | | X | | X | | X[p] | | X | X | | | X | X |
| Assessment/ worsening of HF | | X | | | X | | | | X | | | X | | | X | |
| Concomitant Medications | X | X | | | X | | | | X | | | X | | | X | X |
| Adverse Events | | | X | X | X | X | X | | X | | X | X | | X | X | |
| Hospital Readmissions | | | | | | | | | | | | | | | | X |

*Note*: Day 1 is the day of randomization. Final visit is at Day 30.
[a]Women of childbearing potential only.
[b]Part A only.
[c]Analysed by central reader.
[d]At 12 h only.
[e]From the start of screening (ICF signed), subjects who are to be included in the study should be in a unit where there is real-time telemetry and close medical supervision.
[f]Continuous monitoring up to 24 h prior to dosing, and from pre-dose through 72 h post-dose.
[g]Subjects in Part B will be required to have a pulmonary artery catheter in place prior to randomization. Additional haemodynamic measurement will be required if the subjects become hypotensive, bradycardic, congested or haemodynamically unstable.
[h]Measured at 3, 6, 12 and 18 h.
[i]Measured at 48 and 54 h.
[j]If no central venous line, administration should be no more distal than antecubital vein.
[k]BP measured as described in study/pharmacy manual.
[l]Measured hourly during screening and at pre-randomization. Change in SBP in last two pre-randomization measurements cannot have decreased by >7 mmHg in order to qualify.
[m]For Part A: Measured at 0.5 and 1 h, then hourly to 30 h after infusion start, and then at 32, 34, 36, 40, 44 and 48 h. For Part B: measured hourly from pre-dose to 24 h after infusion start, and then every 2 h through 32 h; every 4 h from 32 to 48 h; hourly from 48 to 66 h; and at 72, 84 and 96 h.
[n]Measured at 1, 2, 3, 4, 5, 6, 12 and 18 h after infusion start.
[o]Collected from 0 to 24 h, from 24 to 48 h, and from 48 to 72 h.
[p]For Part A: blood samples at 6, 12 and 24 h after infusion start and 0.25, 0.5, 1, 6, 12, and 24 h after infusion end. For Part B: blood samples at 6, 12, 24, 36, 48, 52, 56 and 60 h after infusion start and 12, 36 and 48 h after infusion end and at discharge.

(an ECG performed within 3 h before the subject signed informed consent can be accepted) will be recorded and repeated as shown in *Table* 2. Blood pressure is measured hourly from the first hour to 24 h after infusion start; then every 2 h through 32 h; every 4 h from 32 to 48 h; hourly from 48 to 66 h; and then at 72, 84 and 96 h, as well as Day 30.

To be eligible, SBP was assessed on two separate measurements during the last 2 h prior to randomization and cannot have decreased by >7 mmHg in both measurements. Systolic and diastolic blood pressure should be measured using either an arterial line or a manual sphygmomanometer with the patient in a supine or semi-supine position. Measurements should be taken in the same position during the treatment and immediate post-treatment periods and the method for measuring blood pressure (arterial line or manual) should remain the same for the first 24 h. An automated sphygmomanometer should not be utilized because measures of lower blood pressures may be inaccurate. If measured using a sphygmomanometer, blood pressure should be measured carefully in both arms at each time point by first using palpation to estimate the SBP, inflating the cuff to 30 mmHg above the palpated SBP, and slowly (e.g., 2 mmHg/s) releasing the pressure; the average systolic and diastolic blood pressures for both arms will be taken as the measures at the time point.

### *Holter monitoring*

Continuous arrhythmia monitoring via a Holter monitor is collected immediately after informed consent through randomization and from the start of infusion to 72 h. Holter monitor readings were read centrally.

### *Invasive haemodynamics*

All subjects in Part B were required to have a pulmonary artery catheter (e.g., Swan-Ganz) in place before randomization (optional in Part A). Invasive haemodynamic measurements, including cardiac output (CO), systemic vascular resistance, venous oxygen saturation ($SvO_2$), right atrial pressure (RAP), pulmonary artery pressures and pulmonary capillary wedge pressure (PCWP), are collected after randomization and before study drug administration and at Hours 3, 6, 12, 18, 24, 48, 54 and 60 after study drug initiation. Cardiac power (CP) output in Watts will be derived from reported values of mean arterial pressure (MAP), RAP and CO as (MAP − RAP) * CO/451, and will be included among the haemodynamic parameters examined. Some haemodynamic measurements will be documented by monitor tracing of pressures, wedging and thermodilution measurements.

### *Echocardiography*

An echocardiogram confirming ejection fraction ≤40% and no evidence of other pathology to confound interpretation of cardiac physiology was required to qualify the subject for the study. After baseline echocardiograms are then required at Hours 12, 24, 36, 48, 60 and 72 h. Anonymized echocardiographic images are transferred to a central laboratory for formal assessments. Images are acquired during quiet or suspended respiration in the following views: parasternal long and short axis; apical 2-, 3-, 4- and 5-chamber; and subcostal.

### *Physical examination—HF signs and symptoms*

Investigators rate the severity of HF signs and symptoms (rales, orthopnoea, oedema, New York Heart Association class and jugular venous pulse) on ordinal scales pre-dose and at Hours 24, 48, 72 and 96. In-hospital worsening HF (WHF) is defined as worsening signs and/or symptoms of HF since the previous assessment that requires an intensification of intravenous therapy for HF or mechanical ventilatory, renal or circulatory support.

### *Laboratory*

Standard blood chemistry [electrolytes, liver function tests, creatinine, urea or BUN, glucose, albumin, protein and estimated glomerular filtration rate (eGFR)] and haematology (complete blood count with differential) are obtained locally at screening; daily at 24, 48, 72 and 96 h; and at Day 30. A digoxin assay was performed at screening. A serum pregnancy test (β-hCG) for females of childbearing potential is performed at screening and Day 30. Biomarkers, including BNP or NT-proBNP, troponin I or T and venous lactate are measured locally at the investigator's institution at screening; pre-dose; at 12, 24, 48, 72 and 96 h; and at Day 30.

Blood samples are taken pre-dose and at 12, 24, 48, 72 and 96 h post-infusion initiation and at Day 30 and stored frozen locally until shipment to a central laboratory for analysis of cardiac troponin T, BNP, NT-proBNP and potentially other neurohormonal or inflammatory biomarkers.

## Outcome measures

The study's primary efficacy endpoint is the SBP area under the change from baseline curve (AUC) from baseline to Hour 6 in the combined SEISMiC Parts A and B population.

Key secondary efficacy endpoints include the SBP AUC through Hour 24 in Parts A and B combined and the SBP AUC through Hours 12, 24, 48 and 60 in Part B alone.

For analyses of other endpoints combining Parts A and B, only patients from Part A who received a maximum of 1.0 μg/kg/min istaroxime or concurrent placebo ('Part A-1.0') will be included. Other secondary (tertiary/exploratory) efficacy endpoints include the following:

- Changes in SBP and DBP at 6, 12 and 24 h in Parts A and B combined; and at 6, 12, 24, 48 and 60 h in Part B;
- Changes in MAP and heart rate at 12, 24, 48, 72 and 96 h in Parts A and B combined and in Part B;
- Treatment failure through 24 h for Parts A-1.0 and B combined and through 48 h and Day 5 in Part B;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- Changes in PCWP and other invasive haemodynamic parameters from baseline to 3, 6, 12, 18, 24, 48, 54 and 60 h in Part B;
- Changes in echocardiographic measurements at 24 h in Parts A-1.0 and B combined and at 24, 36, 48, 60 and 72 h in Part B;
- Changes in symptoms and signs of congestion at 96 h in Part B;
- Changes in eGFR at 24, 48, 72 and 96 h in Parts A-1.0 and B combined and in Part B;
- Changes in BNP, NT-proBNP, troponin and venous lactate at 12, 24, 48, 72 and 96 h in Parts A-1.0 and B combined and in Part B;
- Composite of WHF adverse event (AE), HF readmission or death to Day 30 in Parts A-1.0 and B combined and in Part B;
- Treatment failure score through 24 h in Parts A-1.0 and B combined and through 60 h in Part B. The treatment failure score is defined as 1 = died; 2 = required circulatory, respiratory or renal mechanical support or discontinued study treatment due to an AE; 3 = treated with iv inotrope or vasopressor; 4 = any SBP more than 10 mmHg below baseline in two consecutive measurements, 5 = any SBP between 5 and10 mmHg below baseline in two consecutive measurements; 6 = none of the above occurred.
- Increase in SBP $\geq$ 5% and $\geq$10 mmHg between 4 and 6 h after study drug initiation and at least one other measurement showing a $\geq$5% increase and a $\geq$10 mmHg change separated by $\geq$2 h during the 60 h infusion for Part B;
- Other clinical outcomes including WHF AE through Day 30 from randomization; WHF event through Day 5; HF readmission through Day 30; all-cause hospital readmission through Day 30; and death through Day 30 in Parts A-1.0 and B combined and in Part B;
- Stay in intensive care unit/cardiac care unit, length of initial hospitalization through Day 30 in Parts A-1.0 and B combined and in Part B;
- Days alive out of the hospital and days alive out of acute care through Day 30 in Parts A-1.0 and B combined and in Part B.

Safety endpoints include the following in Part B:

- Frequency of AEs and serious AEs (SAEs) through Day 30;
- Changes in vital signs, including weight, body temperature, oxygen saturation and urine output;
- Changes in electrocardiogram measurements from baseline to Hours 12, 24, 48, 72, 96 and Day 30;
- Clinically significant arrhythmias (arrhythmias requiring intervention) for a total of 72 h from the start of infusion as determined by a Holter monitor (during the infusion and after the infusion has been stopped);
- Shifts in physical examination from screening to final follow-up;
- Changes in local laboratory results.

## Statistical considerations

Given that this is an estimation study, it was not powered to achieve statistical significance. However, based on the results from previous trials, it is expected that qualitative improvements for patients treated with istaroxime will be seen versus those in the placebo group. Therefore, while formal hypotheses will not be used, appropriate statistical testing will be used for the primary and secondary efficacy endpoints to determine if statistical significance was achieved for the null hypothesis that there is no difference between different treatments. Statistical tests will not be performed for safety analyses.

Primary analyses of the primary and key secondary endpoints will be based on a modified intent-to-treat population, defined as subjects who received treatment (any istaroxime or placebo infused to patient) and had at least one post-baseline blood pressure assessment, and presented according to assigned (randomized) treatments. Safety assessments will be based on a safety population, defined as all subjects who received any study medication, comparing all active (patients who received either active dose of istaroxime) versus placebo subjects in Part B. Subjects will be included in the treatment group for the treatment actually received (if different from the group that they were randomized).

Selected analyses will be performed in Parts A and B combined comparing pooled active treatment group (patients who received any active dose of istaroxime) vs. placebo. Analyses will be performed in subjects enrolled in Part B, comparing pooled treatment groups (istaroxime vs. placebo) as well as individual treatment groups (each of two istaroxime groups vs. placebo group). To account for potential variation in the study populations from Parts A and B, combined analyses will be stratified by study part. Analyses for Part A were stratified by 'pooled' site. Analyses for Part B alone will include site stratification, with sites pooled as Poland versus other country.

The primary endpoint, the SBP AUC through Hour 6 combining all values from Parts A and B, will be computed by trapezoidal rule after applying any applicable imputation. Analyses including only subjects enrolled in Part B will be performed also. Missing values at timepoints prior to an intercurrent event, defined as (1) death, (2) requirement for rescue therapy or (3) study drug discontinuation due to an AE, where values are available prior to and after the timepoint will be imputed using linear interpolation, thus achieving monotone missingness and a monotone imputed regression method can be applied, where missing values over time are imputed sequentially. Values following an intercurrent event will be set to missing and then all remaining missing values imputed using values within the same treatment group. If few values are missing, single imputation will be employed. For the combined analysis, the mean SBP AUC through Hour

6 will be compared between pooled treatment groups using an ANCOVA model including the effects of study part, baseline SBP and treatment group. The model for Part B will include the effects of pooled site, baseline SBP and treatment group. To assess the effect of imputation of missing data, a sensitivity analysis will be conducted using available data. The AUC will be computed up to the last available data within 6 h, including data after an intercurrent event. Analyses of key secondary efficacy endpoints (SBP AUCs to Hours 12, 24, 48 and 60) will be analysed similarly. Efficacy analyses using values imputed in the same way will be performed for vital signs, invasive haemodynamic parameters, echocardiographic parameters and biomarkers; analyses of observed values will also be performed.

Least-square mean changes in longitudinal continuous measures will be estimated from mixed models for repeated measures that include the effects of pooled site, baseline value, treatment group, timepoint and treatment-by-timepoint interaction for Part B alone; and the combined analysis will include study part rather than pooled site. Active and placebo groups will be compared using appropriate contrasts. Values for BNP, NT-proBNP and troponin will be log-transformed for analysis; exponentiated least-square mean changes represent the ratio (i.e., geometric mean ratios) of the post-baseline value over the baseline value after adjustment while the exponentiated LS–mean treatment differences represent the treatment ratio relative to placebo for transformed parameters (i.e., the ratio of the geometric mean ratios).

Treatment groups will be compared with respect to dichotomous outcomes (e.g., treatment failure, increase in SBP $\geq$5% and $\geq$10 mmHg, composite endpoint and other clinical outcomes) using Cochran–Mantel–Haenszel (CMH) tests controlling for pooled site for Part B and using the CMH test controlling for study part for the combined analysis. Results of unstratified analyses may be presented if there are few events, resulting in overly sparse strata.

Ordinal measures (e.g., treatment failure score, length of stay, days alive out of hospital) will be compared between treatment groups using a win odds comparing treatment groups stratified by study part for combined Parts A and B, and stratified by pooled site for Part B, estimated as described in Kawaguchi and Koch.[25] Where appropriate (e.g., HF signs and symptoms), adjustment for baseline response will also be made.

AEs with an onset through Day 30 will be coded using MedDRA version 22.1 or later and incidence presented by system organ class and preferred term.

An interim analysis was reviewed by the Data Monitoring Committee after 10 patients had been enrolled in Part B. Analyses were conducted by an unblinded statistician not employed by the sponsor.

All tests will be two-tailed with 95% confidence intervals ($\alpha$ level of 5%). Analyses will be performed using SAS® System for Windows™, version 9.4 or higher (SAS Institute, Cary, NC, USA) or R version 4.2.3 or higher (R Foundation for Statistical Computing, Vienna, Austria).

## Discussion

In SEISMiC Part A, study patients with SCAI B CS were treated for up to 24 h with istaroxime doses of 1.0–1.5 μg/kg/min. The study results suggested that istaroxime may improve both SBP and cardiac output simultaneously.[23] However, the results also suggested that patients treated with 1.5 μg/kg/min had a tendency towards less favourable biomarker profiles and more WHF events[24]. The results of SESIMiC A have suggested that Istaroxime has not arrhythmogenic side effects and is not associated with any effects to suggest excessive vasoconstriction or redistribution of blood flow such as mesenteric ischaemia, renal impairment or cardiac/cerebral ischaemia. Istaroxime has a short half-life ($<$1 h) and is given by continuous infusion. A terminal metabolite of istaroxime has a longer half-life, approximately 14 h, and is a selective SERCA2a activator. Longer dosing may provide the potential to assess isolated SERCA2a activation in humans.

As a result of these analyses, the SEIMSiC Part B was designed. In this study, patients are administered doses of istaroxime of either 1.0, then 0.5, then 0.25 μg/kg/min for 60 h or 0.5 μg/kg/min for 48 h. In addition to assessing the effects on SBP, the purpose of the study is to assess the haemodynamic effects of istaroxime in more detail, specifically focusing on assessing the exact effects on central haemodynamics: cardiac output, pulmonary artery pressure, and wedge pressure, $SVO_2$ and CP. In addition, in the current study, we will also assess echocardiographic measures and arrhythmia burden as assessed by centrally read Holters.

Notably, the study population mirrors patients with HF-related CS as defined recently.[26,27] Of HF-CS subtypes, the SEISMiC population represents ADHF-CS, patients with a history of cardiac dysfunction or HF who develop significant deterioration. The rate of progression in this phenotype is lower than in AMI-CS, allowing a larger therapeutic window.[28]

To date, patients at risk of CS and with developing CS are treated with either vasoactive/inotropic drugs or mechanical support with devices.[29,30] Intravenous medications developed for the support of patients with CS, such as norepinephrine, milrinone and dobutamine, are limited by both incomplete haemodynamic effects (either increasing blood pressure or increased cardiac output but not both simultaneously) as well as substantial side effects.[12,13,30,31] This has led to those drugs being shown to not improve outcomes in patients with CS and some suggestions to worsening of such events, especially in those with AHF-related shock.[11,12] Mechanical devices have also been shown to have significant

side effects that may limit their efficacy.[32] For instance, the Impella device, which was recently shown to reduce mortality in patients with CS, was also found to be associated with more AEs, especially vascular complications, bleeding and renal impairment related to haemolysis.[32] It is also interesting that the Impella use in CS was related to the increase of CP and CP index (CPI) of 0.39 W [95% confidence interval (CI): 0.24, 0.54], ($P$ = 0.01) and 0.22 W/m$^2$, respectively.[33] This holds promise for pharmacotherapy to be equally effective, less invasive and thus associated with fewer severe complications.[34] Therefore, a drug that can be administered to patients with CS that improves organ perfusion, blood pressure, cardiac output and CP and reduces filling pressures without significant AEs in patients with CS is urgently needed.

The present study will evaluate the effects of istaroxime administered up to 60 h on these haemodynamic, echocardiographic and biomarker variables as well as safety in patients with SCAI B CS. From a clinical standpoint, it seems to be crucial to be able to stop or even reverse the progression of the CS development. It is well established that untreated patients with severe hypotension and hypoperfusion develop the more advanced stages of CS[3] that are related to significantly worse outcomes. Importantly, the more advanced the haemodynamic, perfusion and biochemical disturbances, the harder it becomes to prevent the patient from progressing to stages from which recovery may no longer be possible. This is why it seems so important to have medications in the arsenal to improve blood pressure and perfusion, thereby effectively preventing disease progression.

To conclude, the SEISMiC study will contribute to our understanding of the role of istaroxime in pre-CS patients and potentially provide insight into the drug's haemodynamic effects and safety in this population.

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## Conflict of interest statement

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