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ORIGINAL ARTICLE

Haemodynamic effects of istaroxime in SCAI stage B HF-related cardiogenic shock: Insights from the SEISMiC trial

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Abstract

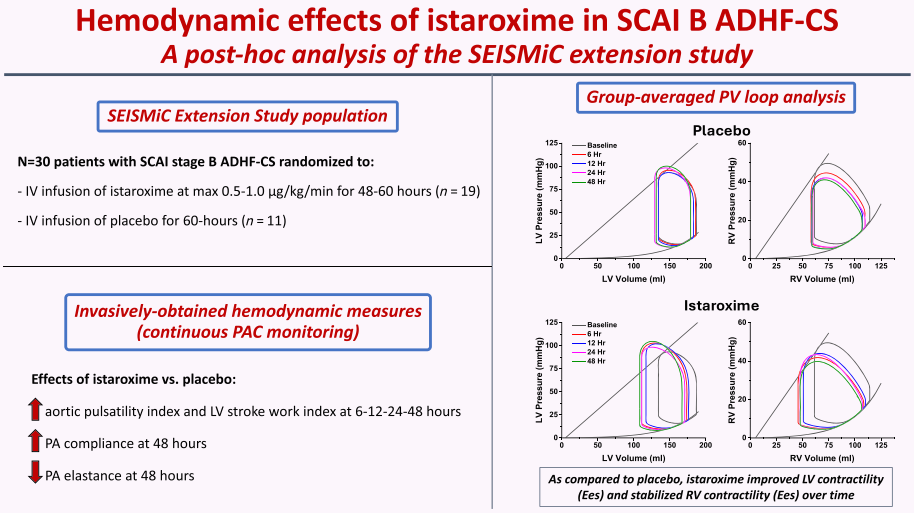
Aims The haemodynamic effects of istaroxime in SCAI stage B cardiogenic shock (CS) due to acute decompensated heart failure (ADHF) have not been evaluated. We assessed the impact of istaroxime on specific invasively-obtained haemodynamic measures.

Methods and results In the SEISMiC extension study, 30 patients with ADHF-related SCAI stage B CS were randomized to 60-h intravenous infusion of either placebo (n = 11) or istaroxime at maximum 0.5–1.0 μg/kg/min (n = 19). In this *post hoc* analysis, invasively-obtained haemodynamic measures, simulated group-averaged pressure-volume (PV) loops, and end-systolic elastance (Ees), derived from individual-patient PV relationships, were compared between istaroxime- and placebo-treated patients. Compared with placebo, patients randomized to istaroxime for 48–60 h had greater increases in aortic pulsatility index (API) and left ventricular (LV) stroke work index (LVSWI) at 6, 12, 24, and 48 h; and greater increase in pulmonary artery (PA) compliance and reduction in PA elastance at 48 h. At group-averaged PV loop analysis, LV contractility remained stable and right ventricular (RV) contractility tended to deteriorate over time with placebo, whereas LV contractility improved and RV contractility tended to be stabilized with istaroxime. Greater increases in both LV Ees and RV Ees were observed with istaroxime versus placebo from baseline to 48 h.

Conclusions In patients with ADHF-pre-CS, istaroxime at doses up to 1.0 μg/kg/min for up to 60 h was associated with sustained improvements in measures of LV performance (API and LVSWI), in parallel with increase in PA compliance and reduction in PA elastance at 48 h. As compared with placebo, istaroxime improved LV contractility and preserved RV contractility, which deteriorated on placebo, over time.

Graphical Abstract

Among patients with ADHF-related SCAI stage B CS enrolled in SEISMiC, istaroxime at doses up to 1.0 μg/kg/min for up to 60 h was associated with sustained improvements in aortic pulsatility index and LV stroke work index, and with increase of PA compliance and reduction in PA elastance at 48 h. At PV loop analysis, LV contractility remained stable and RV contractility tended to deteriorate over time with placebo, whereas LV contractility improved and RV contractility was stabilized with istaroxime.



Keywords Calcitrope; Cardiogenic shock; Haemodynamics; Inotrope; Istaroxime; Pre-cardiogenic shock

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Introduction

Cardiogenic shock (CS) remains associated with a high rate of mortality, and interventions that improve tissue perfusion and blood pressure without a significant risk of adverse events are needed in both overt CS and pre-CS.[1,2] Istaroxime, an androstenedione derivative not chemically related to cardiac glycosides, has both inotropic and lusitropic effects by inhibiting Na^+/K^+-ATPase activity and by activating sarcoplasmic reticulum calcium ATPase isoform 2a (SERCA2a).[3,4] The SEISMiC randomized study was designed to assess the ability of istaroxime to increase systolic blood pressure (SBP), as compared with placebo, in patients with Society for Cardiovascular Angiography and Interventions (SCAI) stage B CS due to acute decompensated heart failure (ADHF) without acute coronary syndrome (ACS).[5,6] In the first part of the SEISMiC study ('Part A'), intravenous istaroxime administered at maximum doses of 1.0 or 1.5 μg/kg/min over 24 h improved SBP, but the higher dose was associated with a trend towards more worsening heart failure events.[5,7] In the subsequent SEISMiC extension trial ('Part B'), administration of istaroxime at doses up to 1.0 μg/kg/min for up to 60 h, compared with placebo, was associated with increased SBP, cardiac output (CO), and mixed venous oxygen saturation (SvO_2), as well as reduced pulmonary capillary wedge pressure (PCWP) and heart rate, without a higher risk of arrhythmias or other safety concerns.[8] Further evaluation of the haemodynamic effects of istaroxime in patients with ADHF-related SCAI stage B CS is of particular interest to better understand its impact on left ventricular (LV) and right ventricular (RV) performance in this setting.

Therefore, in this *post-hoc* analysis of the SEISMiC extension trial, we examined the effects of istaroxime on additional haemodynamic measures and LV and RV contractility based on estimated pressure-volume (PV) analysis.

Material and methods

Study design

The design of the SEISMiC study has been described previously.[5,6,8] In brief, SEISMiC was a pilot, multinational, multicentre, randomized, placebo-controlled safety and efficacy trial. Patients were sequentially enrolled in two parts

('Part A' and 'Part B') under a single protocol. In the SEISMiC extension study (i.e., 'Part B'), patients aged 18 to 85 years hospitalized for ADHF with persistent hypotension (SBP 70–100 mmHg for ≥2 h), heart rate 75 to 150 b.p.m., evidence of congestion on chest X-ray or lung ultrasound, N-terminal pro-B-type natriuretic peptide (NT-proBNP) ≥ 1400 pg/mL, and LV ejection fraction ≤40% were eligible. Included patients must not have taken intravenous vasopressors, inotropes or digoxin in the past 6 h, and patients with venous lactate >2 mmol/L were excluded. Only patients with SCAI stage B CS were therefore enrolled in the study.[9,10] Within 36 h of hospital admission, 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. All patients in 'Part B' underwent invasive haemodynamic monitoring through a pulmonary artery catheter (PAC), and invasive measures were collected before study drug administration (after randomization) and at 3, 6, 12, 18, 24, 48, 54 and 60 h after study drug initiation. Centrally-evaluated continuous arrhythmia monitoring (Holter) was performed up to 72 h. Echocardiography was performed at baseline and at hours 12, 24, 36, 48, 60 and 72 h; anonymized echocardiographic images were transferred to a central laboratory for formal assessments. Echocardiographic data are reported in the previous analyses, but not in the present manuscript.[6,8]

The study was conducted in accordance with the Declaration of Helsinki. Approvals from the 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).

Definitions and endpoints

The following invasive measures were obtained during haemodynamic monitoring (PAC) at the different time-points and were already reported: CO, systemic vascular resistance (SVR), SvO_2, right atrial pressure (RAP), PCWP and systolic, diastolic and mean pulmonary artery pressures (PAP).[6,8] This report focuses on the following additional haemodynamic measurements: aortic pulsatility index (API), left ventricular stroke work index (LVSWI), pulmonary artery (PA) compliance, PA elastance (Ea), PA pulsatility index, and right ventricular stroke work index (RVSWI). API was calculated as pulse pressure divided by PCWP. LVSWI was calculated as 0.0136 × (mean arterial pressure − PCWP) × stroke volume index. PA compliance was calculated as stroke volume divided by PA pulse pressure. PA elastance (Ea) was estimated as systolic PAP divided by stroke volume. PA pulsatility index was calculated as PA pulse pressure divided by RAP. RVSWI was calculated as 0.0136 × (mean PAP − RAP) × stroke volume index. All these variables were calculated at baseline (pre-dose) and 6, 12, 24, 48 and 60 h.

Based on invasive haemodynamic and echocardiographic measures, group-averaged LV and RV pressure-volume loops were also estimated at baseline and 6, 12, 24 and 48 h with the Harvi simulation platform (Harvi Dynamics, Inc. Remsenburg, NY) as detailed previously.[11–13] In brief, values of heart rate, LV ejection fraction, CO, central venous pressure, systolic and diastolic PAP, PCWP and aortic systolic and diastolic pressures serve as inputs to a fitting algorithm that adjusts cardiovascular parameters to simultaneously match all of these values (i.e., the algorithm creates a digital twin). In addition to generating group-averaged pressure-volume loops, this algorithm yields values for a multitude of cardiovascular parameters; for purposes of this study, the most important were LV and RV end-systolic elastances (Ees, i.e., the slope of the respective end-systolic pressure-volume relationships) and stressed blood volume (SBV).[13] LV and RV Ees values and SBV were also derived from haemodynamics of individual patients at baseline and 6, 12, 24, 48 and 60 h.

Statistical analysis

Analyses were based on a modified intention-to-treat population, as described previously.[5,6,8] All analyses were performed comparing all treatment subjects (i.e., all patients who received either dose of istaroxime) to placebo subjects in 'Part B'.

Longitudinal continuous haemodynamic measures were presented as mean ± standard deviation, median (interquartile range) and range, and least-square (LS) mean changes in these measures were estimated from mixed models for repeated measures (MMRMs) including the effects of baseline value, pooled site (Poland vs. other country), treatment group, timepoint and treatment-by-timepoint interaction. Analyses were repeated after imputation of missing values. Missing values flanked by non-missing values were imputed through linear interpolation; values after initiation of rescue therapy were set to missing and then missing values, including missing values following death, were imputed from the prior four values using linear regression in the same treatment group.

The additional longitudinal continuous measures derived from pressure-volume analysis in individual patients (i.e., LV Ees, RV Ees and SBV) were calculated after imputation of missing values, performed as described above. These measures were compared between the istaroxime and placebo arms using a non-parametric approach with adjustment for pooled site (Poland vs. other country) and baseline value, and treatment effects were reported as win odds (WO) with 95% confidence intervals (CI) (i.e., WO > 1.0 if the odds of improvement in that measure on istaroxime are greater than on placebo).

Statistical tests and CIs are two-tailed at alpha 0.05. Analyses were performed using SAS® System for Windows™, version 9.4 or higher (SAS Institute, Cary, NC) or R version

4.2.3 or higher (R Foundation for Statistical Computing, Vienna, Austria).

Results

A total of 30 patients with ADHF-related SCAI stage B CS were randomized in the SEISMiC extension study ('Part B') between 13 December 2023 and 3 September 2024, at 9 participating centers in North America, South America and Europe. Among them, 19 patients were randomized to istaroxime (10 patients initiated at 1.0 μg/kg/min with subsequent dose reduction to 0.25 μg/kg/min over 60 h, and 9 patients received istaroxime at 0.5 μg/kg/min for 48 h followed by placebo) and 11 patients were randomized to placebo for 60 h. Baseline characteristics of the patients enrolled in the SEISMiC extension study have been described previously, as well as the effects of istaroxime versus placebo on SBP (LS mean difference in area under the curve [AUC] of SBP change through 6 h 38.8 mmHg*h, 95% CI 1.3 to 76.2, P = 0.043), CO (LS mean difference in AUC of CO change through 48 h 31.6 L/min*h, 95% CI 6.2 to 56.9, P = 0.017), PCWP (LS mean difference in AUC of PCWP change through 48 h −181.1 mmHg*h, 95% CI −286.9 to −75.3, P = 0.002), systolic PAP (LS mean difference at 48 h −3.31 mmHg, 95% CI −10.40 to 3.75, P = 0.345), diastolic PAP (LS mean difference at 48 h −1.71 mmHg, 95% CI −5.82 to 2.40, P = 0.402), mean PAP (LS mean difference at 48 h −2.05 mmHg, 95% CI −6.67 to 2.58, P = 0.372), SvO_2 (LS mean difference at 48 h 10.0%, 95% CI 6.4 to 13.6, $P < 0.0001$), RAP (LS mean difference at 48 h −1.80 mmHg, 95% CI −3.98 to 0.38, P = 0.102), and SVR (LS mean difference at 48 hours −335 dynes/s/cm^5, 95% CI −709 to 39, P = 0.077).[8]

Effects on haemodynamic parameters

Compared with placebo, patients randomized to istaroxime had greater increases in API at 6 h (LS mean difference 1.91, 95% CI 1.13 to 2.69, $P < 0.0001$), 12 h (LS mean difference 1.13, 95% CI 0.58 to 1.68, P = 0.0002), 24 h (LS mean difference 1.18, 95% CI 0.41 to 1.95, P = 0.0042), and 48 h (LS mean difference 1.99, 95% CI 1.04 to 2.94, P = 0.0002). Similarly, greater increases in LVSWI were observed during istaroxime infusion as compared with placebo at 6 h (LS mean difference 7.75 g*m/m^2, 95% CI 2.01 to 13.49, P = 0.0100), 12 h (LS mean difference 7.66 g*m/m^2, 95% CI 3.57 to 11.75, P = 0.0007), 24 h (LS mean difference 5.30 g*m/m^2, 95% CI 0.60 to 10.00, P = 0.0284), and 48 h (LS mean difference 8.12 g*m/m^2, 95% CI 3.66 to 12.57, P = 0.0009). Patients randomized to istaroxime had greater increase in PA compliance at 48 h as compared with placebo (LS mean difference 0.94 mL/mmHg, 95% CI 0.11 to 1.76, P = 0.0269), whereas no significant differences were observed between treatment arms at the other time-points. Istaroxime-treated patients also had a greater reduction in PA elastance (Ea) at 48 h (LS mean difference −0.35 mmHg/mL, 95% CI −0.58 to −0.12, P = 0.0046), whereas no significant differences were observed between treatment arms at the other time-points. No significant differences in PA pulsatility index and RVSWI were seen between istaroxime-treated and placebo-treated patients. All results are summarized in *Table 1*. The results were consistent after including imputed values (*Tables S1–S6*).

Effects on PV loops, end-systolic elastance (Ees) and SBV

Estimated group-averaged pressure-volume loop analyses are depicted in *Figure 1*. In patients receiving placebo, minimal changes in estimated LV Ees were observed from baseline to 48 h, whereas RV Ees tended to decrease over time. In patients receiving istaroxime, LV Ees increased from baseline up to 48 h, whereas RV Ees was nearly unchanged at the different time-points.

Results of the individual patient-based pressure-volume analysis showed greater increases in LV Ees were observed during istaroxime infusion as compared with placebo at 6 h (WO 4.53, 95% CI 3.04 to 7.77, $P < 0.0001$), 12 h (WO 3.19, 95% CI 2.04 to 5.76, $P < 0.0001$), 24 h (WO 3.20, 95% CI 2.11 to 5.46, $P < 0.0001$), and 48 h (WO 2.88, 95% CI 1.87 to 5.02, $P < 0.0001$; *Table S7* and *Figures S1–S2*). Compared with placebo, patients randomized to istaroxime also had greater increases in RV Ees at 6 h (WO 1.77, 95% CI 1.11 to 3.04, P = 0.0152), 12 h (WO 1.79, 95% CI 1.24 to 2.68, P = 0.0015), 24 h (WO 1.69, 95% CI 1.10 to 2.72, P = 0.0153), 48 h (WO 1.77, 95% CI 1.16 to 2.86, P = 0.0077), and 60 h (WO 1.68, 95% CI 1.09 to 2.71, P = 0.0177; *Table S8* and *Figures S3–S4*). No significant differences in stressed blood volume were observed between istaroxime-treated and placebo-treated patients at the different time-points (*Table S9*, *Figures S5* and *S6*).

Discussion

This analysis of the multicentre, randomized, placebo-controlled SEISMiC extension trial shows that administration of istaroxime at doses up to 1.0 μg/kg/min for up to 60 h in patients with ADHF-related SCAI stage B CS, as compared with placebo, was associated with sustained improvements in API and LVSWI, and with increase in PA compliance and reduction in PA elastance at 48 h. Moreover, estimated pressure-volume loop analysis suggested that LV contractility remained stable and RV contractility tended to deteriorate over time in patients receiving placebo, whereas LV contractility improved and RV contractility tended to be stabilized in patients receiving istaroxime. Greater increases in both LV

Table 1 Changes in haemodynamic measurements

Parameter/time point	Statistic	Istaroxime ($N = 19$)	Placebo ($N = 11$)		
Aortic pulsatility index (API)					
Pre-dose	*N*	18	11		
	Mean (SD)	1.64 (0.601)	2.04 (1.307)		
	Median	1.55	1.60		
	Min, Max	0.5, 2.6	0.9, 4.6		
		LS-Mean (SE)	**LS-Mean (SE)**	**LS Mean Difference (95% CI)**	***P*-value**
Change from baseline					
Hour 6		1.95 (0.25)	0.04 (0.29)	1.91 (1.13, 2.69)	<0.0001
Hour 12		1.50 (0.18)	0.37 (0.20)	1.13 (0.58, 1.68)	0.0002
Hour 24		1.76 (0.25)	0.58 (0.29)	1.18 (0.41, 1.95)	0.0042
Hour 48		2.36 (0.30)	0.37 (0.36)	1.99 (1.04, 2.94)	0.0002
Hour 60		1.47 (0.40)	1.54 (0.51)	−0.07 (−1.39, 1.25)	0.9168
Left ventricular stroke work index (LVSWI), g*m/m^2					
Pre-dose	*N*	18	11		
	Mean (SD)	17.61 (6.212)	17.05 (6.007)		
	Median	15.21	17.32		
	Min, Max	10.3, 33.0	8.9, 28.6		
		LS-Mean (SE)	**LS-Mean (SE)**	**LS Mean Difference (95% CI)**	***P*-value**
Change from baseline					
Hour 6		9.47 (1.82)	1.72 (2.15)	7.75 (2.01, 13.49)	0.0100
Hour 12		7.52 (1.36)	−0.14 (1.50)	7.66 (3.57, 11.75)	0.0007
Hour 24		7.55 (1.54)	2.25 (1.73)	5.30 (0.60, 10.00)	0.0284
Hour 48		8.99 (1.47)	0.87 (1.62)	8.12 (3.66, 12.57)	0.0009
Hour 60		4.28 (1.61)	5.07 (1.89)	−0.79 (−5.81, 4.23)	0.7502
PA compliance, mL/mmHg					
Pre-dose	*N*	19	11		
	Mean (SD)	2.28 (1.033)	2.39 (1.041)		
	Median	2.17	2.36		
	Min, Max	0.9, 5.0	1.2, 4.2		
		LS-Mean (SE)	**LS-Mean (SE)**	**LS Mean Difference (95% CI)**	***P*-value**
Change from baseline					
Hour 6		0.55 (0.22)	0.26 (0.26)	0.29 (−0.40, 0.98)	0.3971
Hour 12		0.36 (0.18)	0.11 (0.22)	0.25 (−0.32, 0.83)	0.3741
Hour 24		0.59 (0.18)	0.13 (0.21)	0.46 (−0.11, 1.03)	0.1091
Hour 48		0.94 (0.26)	0.00 (0.31)	0.94 (0.11, 1.76)	0.0269
Hour 60		0.57 (0.38)	1.06 (0.49)	−0.49 (−1.77, 0.78)	0.4347
PA elastance (Ea), mmHg/mL					
Pre-dose	*N*	19	11		
	Mean (SD)	1.06 (0.432)	1.06 (0.439)		
	Median	0.88	1.11		
	Min, Max	0.4, 2.0	0.5, 1.8		
		LS-Mean (SE)	**LS-Mean (SE)**	**LS Mean Difference (95% CI)**	***P*-value**
Change from baseline					
Hour 6		−0.29 (0.08)	−0.10 (0.10)	−0.19 (−0.45, 0.06)	0.1308
Hour 12		−0.26 (0.05)	−0.14 (0.06)	−0.13 (−0.28, 0.03)	0.1019
Hour 24		−0.32 (0.07)	−0.15 (0.08)	−0.18 (−0.39, 0.04)	0.1005
Hour 48		−0.38 (0.07)	−0.04 (0.09)	−0.35 (−0.58, −0.12)	0.0046
Hour 60		−0.14 (0.08)	−0.28 (0.10)	0.14 (−0.13, 0.41)	0.2887
PA pulsatility index (PAPi)					
Pre-Dose	*N*	19	11		
	Mean (SD)	3.22 (1.668)	2.14 (1.201)		
	Median	3.22	1.90		
	Min, Max	1.2, 7.4	0.9, 4.4		
		LS-Mean (SE)	LS-Mean (SE)	LS Mean Difference (95% CI)	***P*-value**
Change from baseline					
Hour 6		2.67 (0.80)	0.64 (1.02)	2.03 (−0.63, 4.68)	0.1298
Hour 12		2.68 (0.73)	1.32 (0.91)	1.36 (−1.04, 3.76)	0.2556
Hour 24		3.12 (0.99)	1.49 (1.22)	1.63 (−1.61, 4.86)	0.3108
Hour 48		1.83 (0.48)	1.16 (0.56)	0.67 (−0.85, 2.19)	0.3717
Hour 60		2.31 (1.15)	2.34 (1.45)	−0.03 (−3.83, 3.76)	0.9852

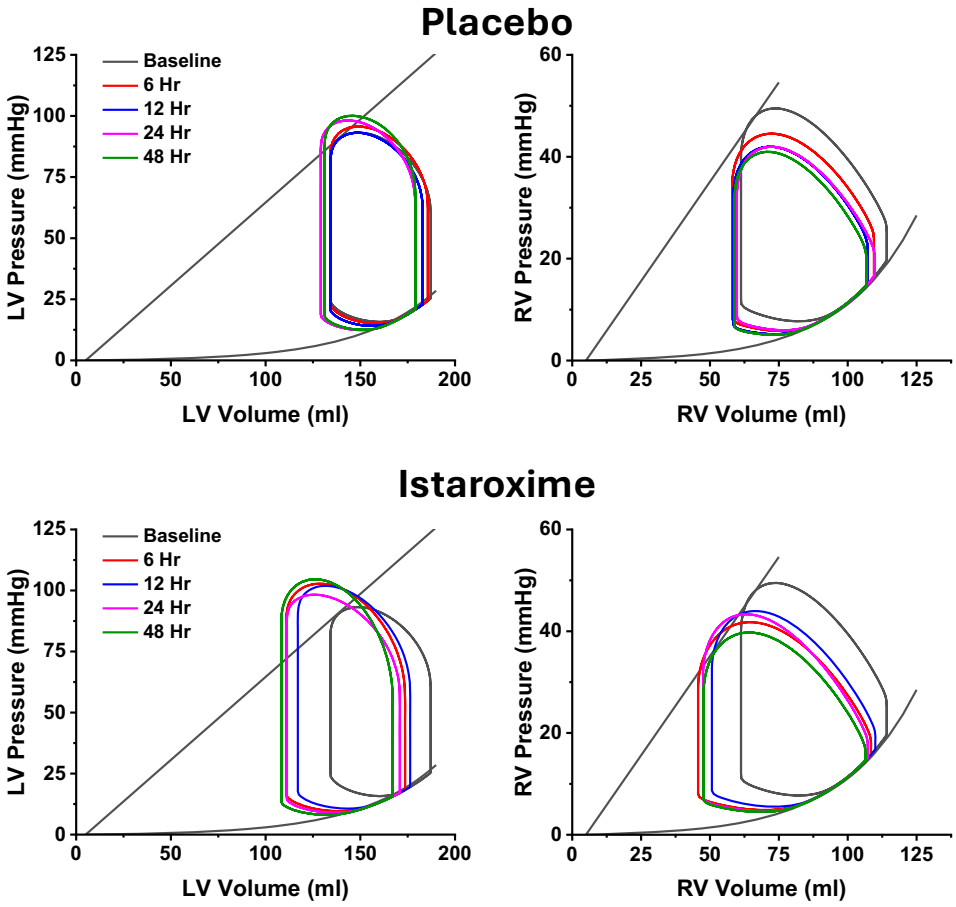
(*Continues*)

Table 1 (continued)

Parameter/time point	Statistic	Istaroxime (N = 19)	Placebo (N = 11)		
Right ventricular stroke work index (RVSWI), g*m/m^2					
Pre-dose	*N*	19	11		
	Mean (SD)	8.49 (3.882)	7.62 (4.414)		
	Median	9.05	6.75		
	Min, Max	3.6, 17.7	2.3, 14.7		
		LS-Mean (SE)	**LS-Mean (SE)**	**LS Mean Difference (95% CI)**	***P*-value**
Change from baseline					
Hour 6		0.89 (0.99)	−0.99 (1.24)	1.88 (−1.35, 5.11)	0.2438
Hour 12		0.46 (0.77)	−1.63 (0.94)	2.09 (−0.37, 4.55)	0.0928
Hour 24		0.65 (0.98)	−0.95 (1.21)	1.60 (−1.57, 4.78)	0.3089
Hour 48		−0.33 (0.77)	−2.17 (0.91)	1.84 (−0.58, 4.26)	0.1303
Hour 60		−1.47 (0.68)	−1.78 (0.82)	0.31 (−1.82, 2.45)	0.7649

Statistics from a mixed model for repeated measures (MMRM) including the effects of baseline value, pooled site, treatment, timepoint, and treatment-by-timepoint interaction.

Figure 1 Estimated group-averaged LV and RV pressure-volume loops by treatment arm. The figure shows estimated group-averaged left ventricular (LV) and right ventricular (RV) pressure-volume loop analysis at different time-points (from baseline up to 48 h) in patients receiving placebo and in those receiving istaroxime.



Ees and RV Ees were observed with istaroxime versus placebo at the analysis of measures derived from pressure-volume relationships in individual patients.

The SEISMiC trial already demonstrated the effects of intravenous administration of istaroxime at doses up to 1.0 μg/kg/min in increasing SBP, CO and SvO_2, as well as in reducing PCWP and heart rate, among patients hospitalized for ADHF-related SCAI stage B CS, without safety concerns.[5,7,8] This *post hoc* analysis further refines the evaluation of the haemodynamic effects of istaroxime versus placebo in patients with SCAI stage B CS (i.e., pre-CS) due to ADHF. Patients with pre-CS are at risk of deteriorating to overt or worsening CS, which is associated with a very high risk of short-term mortality.[10,14] The rate of progression is lower in ADHF-related than in acute myocardial infarction-related CS, thus the therapeutic window is larger in these patients.[15–17] The implementation of therapies improving haemodynamics is particularly important in this window, in order to preserve end-organ function and prevent further deterioration and the need of short-term mechanical circulatory support (MCS). Current intravenous medications for CS are limited by their selective haemodynamic effects or by substantial side effects.[1] Medications with concomitant vasodilatory effects, including type 3 phosphodiesterase inhibitors and possibly levosimendan at high doses, may worsen hypotension when peripheral vasodilation prevails over the increase in cardiac output.[3] In contrast, the increase in SBP, consistently shown after istaroxime in all trials,[6–8,18] makes this drug particularly suited for the treatment of the patients in the pre-shock phase. Beyond its effects on SBP, CO and PCWP, istaroxime improved LV performance in our study, as it was associated with sustained improvements in API and LVSWI up to 48 h as compared with placebo. Of note, API reflects both LV contractility and cardiac filling pressures,[19,20] and LVSWI also incorporates both systolic and diastolic LV function,[21] thus allowing a comprehensive assessment of LV performance. Consistently, estimated group-averaged pressure-volume loop analyses showed that minimal changes in LV Ees occurred in patients receiving placebo, whereas LV Ees increased among istaroxime-treated patients from baseline to 48 h. Greater increases in LV Ees were confirmed with istaroxime versus placebo at 6, 12, 24 and 48 h at the analysis of measures derived from the individual patient-based pressure-volume analysis. These findings confirm the positive inotropic effects of istaroxime when assessed with a load-independent measure of contractility (i.e., Ees[22,23]) among patients with ADHF-related SCAI stage B CS. This increase in LV contractility is achieved without a concomitant increase in heart rate or a significant risk of arrhythmias.[8] Of note, these haemodynamic effects may have relevant implications on the risk of clinical deterioration among patients with ADHF-related pre-CS and, consequently, on the need of MCS and the type of MCS device(s) in case of therapeutic escalation.

As compared with placebo, istaroxime was associated with a greater increase in PA compliance and a greater reduction in PA elastance at 48 h, thus suggesting a reduction in RV afterload with prolonged istaroxime infusion up to 48 h.[24,25] Although no significant differences in PA pulsatility index and RVSWI were observed between istaroxime-treated and placebo-treated patients, estimated group-averaged pressure-volume loop analyses showed that RV Ees tended to decrease in patients receiving placebo whereas it remained stable among istaroxime-treated patients from baseline to 48 h. This suggests that istaroxime may be useful in stabilizing RV contractility and thus preventing its deterioration in patients with ADHF-related SCAI stage B CS. Indeed, at the analysis of measures derived from pressure-volume relationships in individual patients, greater increases in RV Ees were confirmed with istaroxime versus placebo at 6, 12, 24, 48 and 60 h. RV dysfunction is common in patients with overt CS, and haemodynamic parameters reflecting RV performance have a strong prognostic impact in this setting.[26–28] Moreover, RV function has a prognostic incremental role among patients with advanced HF who experience an ADHF event.[29,30] A significant deterioration of RV performance in patients with SCAI stage B pre-CS might also favour the transition to overt biventricular CS, that is associated with a very high risk of mortality.[28,31] Therefore, a treatment preventing RV deterioration in patients with pre-CS due to ADHF, without significant arrhythmic risks or other safety concerns, may be particularly useful. The observed effects of istaroxime in stabilizing RV contractility are added to the marked increases in LV contractility as compared with placebo. Overall, our results extend the benefits observed with istaroxime versus placebo in the main analyses of the SEISMiC study,[5,7,8] and explain the previously reported increase in SBP, CO and SvO_2, as well as the PCWP reduction.[5,7,8] These preliminary findings on the haemodynamic effects of istaroxime in ADHF-related SCAI stage B CS need to be validated in larger studies, potentially including patients with more severe CS.

Study limitations

Beyond the already described limitations of the overall SEISMiC trial,[5,7,8] this analysis has some specific limitations. First, the analyses presented in this study were *post hoc* analyses. Second, some specific analyses might have been limited by some missing values. However, imputation of missing values was also performed to overcome this limitation, and the sensitivity analyses including imputed values were also reported and were consistent with the main analyses. Third, all the results should be interpreted in the context of the SEISMiC study with respect to its inclusion/exclusion criteria, thus our findings cannot be translated to patients with more severe CS.

Conclusions

In the SEISMiC extension trial enrolling patients with ADHF-related SCAI stage B CS, administration of istaroxime at doses up to 1.0 μg/kg/min for up to 60 h was associated with sustained improvements in API and LVSWI, in parallel with an increase of PA compliance and a reduction in PA elastance at 48 h. Estimated pressure-volume loop analysis suggested that LV contractility remained stable and RV contractility tended to deteriorate over time in patients receiving placebo, whereas LV contractility improved and RV contractility tended to be stabilized in patients receiving istaroxime.

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Conflict of Interest

MP received personal fees from Abbott Vascular, AstraZeneca, Bayer, Boehringer Ingelheim, Eli Lilly, Novartis, Novo Nordisk, Roche Diagnostics, Viatris, and Vifor Pharma. GC, BD, and MN are employees of Momentum Research, Inc. which has received grants from 4TEEN4 Pharmaceuticals, Corteria Pharmaceuticals, Echosens, Heart Initiative, Roche Diagnostics Inc., Windtree Therapeutics Inc., and XyloCor Therapeutics. AM reports personal fees from Orion, Roche, Adrenomed, and Fire 1 and grants and personal fees from 4TEEN4, Abbott, Roche, and Sphyngotec. OC is a member of the Boehringer Ingelheim Advisory Board. GF reports lecture fees and/or advisor and/or trial committee membership from Bayer, Boehringer Ingelheim, Servier, Novartis, Impulse Dynamics, Vifor, Medtronic, Cardior, Novo Nordisk; Research Grants from the European Union. PP reports other from Trevena, during the conduct of the study; reports grants and personal fees from Amgen, Inc., grants and personal fees from Servier, grants and personal fees from Boehringer Ingelheim, grants and personal fees from Vifor Pharma, grants and personal fees from Novartis, grants and personal fees from Bayer, grants and personal fees from Cibiem, grants and personal fees from AstraZeneca, grants and personal fees from BMS, grants and personal fees from Renal Guard Solutions, grants and personal fees from Impulse Dynamics, grants and personal fees from Abbott Vascular, personal fees from Berlin Chemie, outside the submitted work. PS, CG, and SS are employees of Windtree Therapeutics, Inc. MM received personal fees of minimal amounts in the last 3 years from Amgen, Livanova, and Vifor Pharma as a member of Executive or Data Monitoring Committees of sponsored clinical trials; from AstraZeneca, Abbott Vascular, Bayer, Boehringer Ingelheim, and Edwards Therapeutics for participation in advisory boards and/or speeches at sponsored meetings. All other authors have nothing to disclose.

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1: Changes in aortic pulsatility index (after inclusion of imputed values).
Table S2: Changes in left ventricular stroke work index (after inclusion of imputed values).
Table S3: Changes in PA compliance (after inclusion of imputed values).
Table S4: Changes in PA elastance (Ea) (after inclusion of imputed values).
Table S5: Changes in PA pulsatility index (after inclusion of imputed values).
Table S6: Changes in right ventricular stroke work index (after inclusion of imputed values).
Table S7: Changes in left ventricular end-systolic elastance (Ees) (after inclusion of imputed values).
Table S8: Changes in right ventricular end-systolic elastance (Ees) (after inclusion of imputed values).
Table S9: Changes in stressed blood volume (after inclusion of imputed values).
Figure S1: Actual values of left ventricular end-systolic elastance at the different time-points by treatment arm.
Figure S2: Changes in left ventricular end-systolic elastance by treatment arm.
Figure S3: Actual values of right ventricular end-systolic elastance at the different time-points by treatment arm.
Figure S4: Changes in right ventricular end-systolic elastance by treatment arm.
Figure S5: Actual values of stressed blood volume at the different time-points by treatment arm.
Figure S6: Changes in stressed blood volume by treatment arm.

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