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ORIGINAL CLINICAL SCIENCE

Safety and efficacy intravenous istaroxime up to 60 hours for patients with pre-cardiogenic shock

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KEYWORDS:
Pre-cardiogenic shock;
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Cardiac calcitrope;
Central hemodynamics;
Acute heart failure;
Intravenous therapy

BACKGROUND AND AIMS: A drug that improves blood pressure and cardiac output (CO) while reducing pulmonary wedge pressure safely is needed for patients with cardiogenic shock (CS) due to acute heart failure (AHF).

METHODS: In a randomized, double-blind, placebo-controlled trial, istaroxime 0.5 to 1.5 μg/kg/min for 24-60 hours was administered to 48 patients, and placebo to 42 patients, with pre-CS due to AHF under hemodynamic monitoring. Echocardiographic and Holter monitoring were done in both parts.

RESULTS: Patients randomized to istaroxime had a greater increase in systolic blood pressure (SBP) during the first 6 hours (primary endpoint), ls-mean (SE) 62.0 (6.59) mmHg*hour vs 36.4 (7.11) in the placebo arm (LS mean difference of 25.6 mmHg*hour, 95% CI 7.2-44.0 mmHg*h, $P = 0.007$). In patients administered istaroxime for at least 48 hours, SBP increase persisted for 60 hours. Istaroxime led to a greater increase in CO (0.66 L/min, $P = 0.017$) and decrease in wedge pressure (3.8 mmHg, $P = 0.0017$). Relative to average baselines of 3.6 L/min for CO and 22.5 mmHg for wedge pressure, this translates into improvements of 18.3% and 16.9%, respectively. Echocardiographic assessments showed improvements in E/A, TAPSE, and LA volume at 24 hours. There were improvements in eGFR at 24-72 hours and NYHA class to 72 hours. NT-proBNP increased more in istaroxime-treated

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patients. Heart rate decreased more in the first 24 hours in istaroxime-treated patients. No significant malignant arrhythmias were detected in patients treated with istaroxime on Holter monitoring.
CONCLUSIONS: In this small study, istaroxime doses of up to 1.0 μg/kg/min for up to 60 hours were associated with improvements in SBP, CO and reductions in wedge pressure and heart rate without increases in arrhythmias.
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Background

Cardiogenic shock (CS) continues to be one of the most known fatal diseases, leading to about 50% mortality after its diagnosis.[1–3] Current vasopressors and inotropes, acting through adrenergic receptor stimulation, are associated with tachycardia, arrhythmias, and, in many studies, poorer outcomes.[2,4–8] To date, a therapy that would simultaneously improve systolic blood pressure (SBP) and cardiac output (CO) while unloading the LV, as assessed by reduction of pulmonary capillary wedge pressure (PCWP), without causing vasodilation, arrhythmias, or increased heart rate has not been discovered. Where patients require combined blood pressure (BP) and CO increases and PCWP decreases, investigators need to resort to mechanical circulatory support devices, most commonly Impella.[9,10] Istaroxime is a derivative of androstenedione and is not chemically related to cardiac glycosides.[11] It works through dual mechanisms of action: 1) by inhibiting 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.[12] This promotes sarcoplasmic reticulum calcium reuptake, thus improving contraction, relaxation (lusitropy), and contractility,[13] expected to have beneficial effects in patients with CS.[14–17]

The SEISMiC study was designed to assess the ability of istaroxime to increase SBP in patients with Stage B Society for Cardiovascular Angiography and Interventions (SCAI) pre-CS[18,19] due to acute decompensated heart failure (ADHF) without acute coronary syndrome.[20] Results for the initial part of the study ("Part A") have already been published.[21,22] The SEISMiC study was extended ("Part B") to further explore the dose response to istaroxime in patients randomized to a 60-hour infusion of one of two lower istaroxime regimens or placebo and also included invasive hemodynamic assessments.[23] Figure 1 illustrates the study schema for SEISMiC Parts A and B, including treatment periods, dosing strategies, and evaluation timepoints.

Methods

Study design

SEISMiC was a pilot, multinational, multicenter, randomized, double-blind, placebo-controlled safety and efficacy study. In Part B, male or female subjects aged 18 to 85 years hospitalized for ADHF with persistent hypotension (SBP 70-100 mmHg for 2 hours) and heart rate 75 to 150 beats/minute, congestion on chest X-ray or lung ultrasound, NT-proBNP ≥ 1400 pg/mL, and left ventricular ejection fraction ≤ 40% were eligible. Patients with SCAI stage B pre-CS were enrolled, whereas those with SCAI stage C or worse, including those with venous lactate > 2 mmol/L, were excluded. Subjects must not have taken intravenous (iv) vasopressors, inotropes, or digoxin prior to enrollment. The detailed list of inclusion/exclusion criteria is given in Supplemental Table 1. Patients were enrolled at seven hospitals in North America, South America, and Europe. More detailed information on the study conduct and rationale is published elsewhere.[23] The study was 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).

Combining SEISMiC A and B for the current analysis

For the current analysis, three types of analysis were done. For the majority of the analysis describing changes to 96 hours only the results from SEISMiC B are presented ($n = 30$), as those were the only patients who were treated for at least 48 hours. For the SBP changes to 6 and 24 hours, as prespecified (see below), results were combined from all the SEISMiC database ($n = 90$). For other analyses examining events and changes in biomarkers, the results of SEISMiC A patients who were treated with 1.0 μg/kg/min or less for 24-60 hours were combined, as those doses were determined in analyzing the results of SEISMiC A to be those that will be explored further for possible clinical use in the future.

Study intervention

Patients were randomized within 36 hours of hospital admission and a maximum of 24 hours following informed consent. In Part B, patients were randomized 1:1:1 within the study site to a 60-hour continuous infusion of either placebo or one of two istaroxime dosing regimens: (1) 1.0 μg/kg/min for 6 hours, 0.5 μg/kg/min for 42 hours, followed by 0.25 μg/kg/min for 12 hours or (2) 0.5 μg/kg/min for 48 hours followed by placebo for 12 hours (Figure 1).

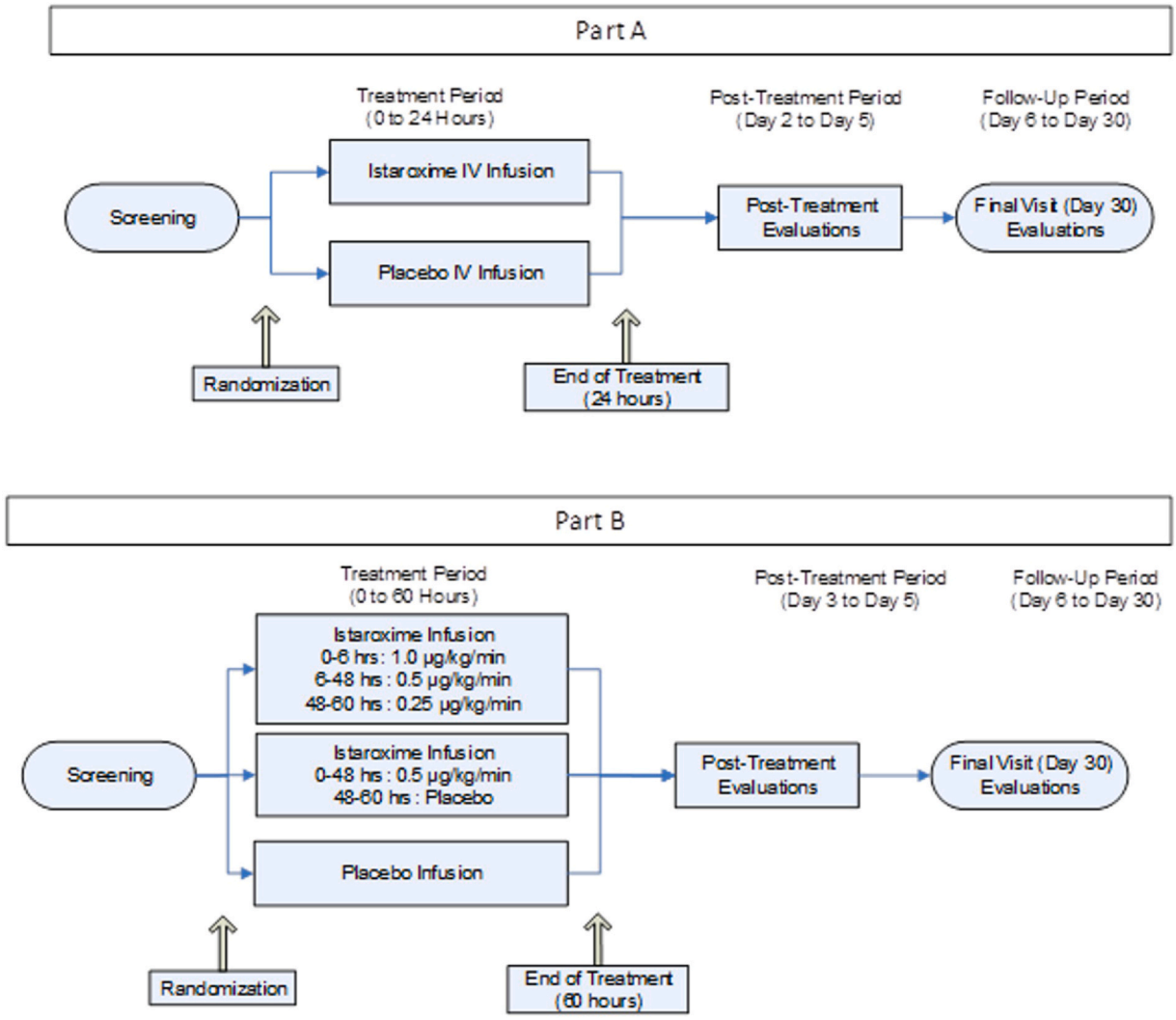

Figure 1 Study schema for SEISMiC A and B.

Concomitant Therapy – are described in Supplemental Text 1.

Study Assessments and Procedures - Study activities were detailed in the design paper.[23] Further details are described in Supplemental Text 1.

Outcome Measures The study's primary efficacy endpoint was the SBP area under the change from baseline curve (AUC) from baseline through hour 6 in the combined SEISMiC Parts A and B population (all patients enrolled, $n = 90$ regardless of dose).

Key secondary efficacy endpoints included 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") were included. A detailed list of all secondary endpoints is presented in the design paper.[23]

Statistical considerations

Primary analyses of the primary and key secondary endpoints were based on a modified intention-to-treat population, defined as subjects who received treatment (any istaroxime or placebo infused to the patient) and had at least one post-baseline BP assessment, and are presented according to assigned (randomized) treatments. Safety assessments were 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) vs. placebo subjects in Part B. Subjects were included in the treatment group for the treatment actually received (if different from the group that they were randomized).

Selected analyses were performed in Parts A and B combined, comparing te pooled active treatment group (patients who received any active dose of istaroxime) vs placebo. Analyses were 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 were stratified by study part. Analyses for Part A were stratified by "pooled" sites. Analyses for Part B alone included site stratification, with sites pooled as Poland vs other country. Further details are described in Supplemental Text 1.[24]

Table 1 Baseline Characteristics of the Patients Enrolled in the SEISMiC B Study

Demographic parameter	Statistic	Istaroxime ($N = 19$)	Placebo ($N = 11$)	Total ($N = 30$)
Age, years	Mean (SD)	64.1 (14.41)	63.4 (12.42)	63.8 (13.50)
Sex				
Male	*n* (%)	17 (89.5%)	10 (90.9%)	27 (90.0%)
Female	*n* (%)	2 (10.5%)	1 (9.1%)	3 (10.0%)
Weight, kg	Mean (SD)	86.99 (22.660)	82.09 (11.335)	85.19 (19.204)
Hypertension	*n* (%)	15 (78.9%)	6 (54.5%)	21 (70.0%)
Hyperlipidemia	*n* (%)	13 (68.4%)	8 (72.7%)	21 (70.0%)
Pacemaker insertion (other than biventricular)	*n* (%)	3 (15.8%)	2 (18.2%)	5 (16.7%)
Cardiac resynchronization therapy (CRT or biventricular pacing)	*n* (%)	8 (42.1%)	3 (27.3%)	11 (36.7%)
Automatic implantable cardioverter-defibrillator (AICD)	*n* (%)	9 (47.4%)	5 (45.5%)	14 (46.7%)
Prior myocardial infarction	*n* (%)	9 (47.4%)	5 (45.5%)	14 (46.7%)
Prior coronary artery bypass graft (CABG)	*n* (%)	3 (15.8%)	3 (27.3%)	6 (20.0%)
Prior percutaneous coronary intervention (PCI)	*n* (%)	8 (42.1%)	6 (54.5%)	14 (46.7%)
Prior cerebrovascular accident (CVA)/Stroke	*n* (%)	3 (15.8%)	1 (9.1%)	4 (13.3%)
Atrial fibrillation	*n* (%)	9 (47.4%)	5 (45.5%)	14 (46.7%)
Atrial Flutter	*n* (%)	2 (10.5%)	0	2 (6.7%)
History of Heart Failure?	*n* (%)	19 (100.0%)	11 (100.0%)	30 (100.0%)
NYHA Class (1 month prior to screening)				
I	*n* (%)	1 (5.3%)	0	1 (3.3%)
II	*n* (%)	2 (10.5%)	4 (36.4%)	6 (20.0%)
III	*n* (%)	13 (68.4%)	5 (45.5%)	18 (60.0%)
IV	*n* (%)	3 (15.8%)	2 (18.2%)	5 (16.7%)
Most recent left ventricular ejection fraction (LVEF)	Mean (SD)	22.6 (8.66)	23.6 (8.30)	23.0 (8.40)
Hospitalized for heart failure in the past year?	*n* (%)	11 (57.9%)	7 (63.6%)	18 (60.0%)
Asthma	*n* (%)	2 (10.5%)	0	2 (6.7%)
Bronchitis	*n* (%)	0	0	0
Pulmonary hypertension	*n* (%)	2 (10.5%)	1 (9.1%)	3 (10.0%)
Chronic obstructive pulmonary disease (COPD)	*n* (%)	2 (10.5%)	0	2 (6.7%)
Cancer	*n* (%)	0	1 (9.1%)	1 (3.3%)
Renal disease	*n* (%)	4 (21.1%)	3 (27.3%)	7 (23.3%)
Renal failure	*n* (%)	1 (5.3%)	1 (9.1%)	2 (6.7%)
History of liver disease	*n* (%)	2 (10.5%)	2 (18.2%)	4 (13.3%)
History of diabetes	*n* (%)	9 (47.4%)	6 (54.5%)	15 (50.0%)

Results

Between 13-Dec-2023 and 03-Sep-2024 30 patients were randomized in Part B in Poland, Italy, United States of America, and Argentina to a 60-hour study drug infusion: 19 to istaroxime (10 patients initiated at 1.0 μg/kg/min and tapering down to 0.25 μg/kg/min over 60 hours, and 9 to istaroxime 0.5 μg/kg/min for 48 hours followed by placebo). Baseline characteristics of the patients enrolled in Part B are presented in Table 1. The mean infusion duration was 58.1 ± 6.87 hours in the istaroxime arm and 59.7 ± 0.68 in the placebo arm.

Effects on SBP

The effects of istaroxime on SBP are presented in Figure 2, as detailed above, they were analyzed in all patient enrolled in the SEISMiC study—all doses and all placebo; $n = 90$. The study met its primary endpoint with an LS mean (SE) SBP AUC through hour 6 in the pooled istaroxime arm of 62.0 (6.59) mmHg*h vs 36.4 (7.11) in the placebo arm (LS mean difference 25.6, 95% CI 7.2-44.0 mmHg*h, $P = 0.007$) in the Parts A and B combined (Figure 2A). The results were 78.4 (11.91) vs 39.6 (13.81) mmHg*h, respectively, in Part B alone (LS mean difference 38.8, 95% CI 1.3-76.2 mmHg*hour, $P = 0.043$) (Figure 2B). Sensitivity analyses where observed data was used showed similar results with an (LS mean difference 25.2, 95% CI 6.8-43.6 mmHg*h, P=0.008) in Parts A and B combined and an (LS mean difference 39.0, 95% CI 1.6-76.4, $P = 0.042$) in Part B alone. Effects of the two different doses of istaroxime (patients treated with 1.0 μg/kg/min in the first 6 hours and patients treated with 0.5 μg/kg/min in the first 6 hours vs placebo) are presented in Supplemental Figure 1.

Effects on other vital signs

Effects on diastolic BP, mean arterial pressure, and pulse pressure are presented in Supplemental Figures 2, 3 and 4.

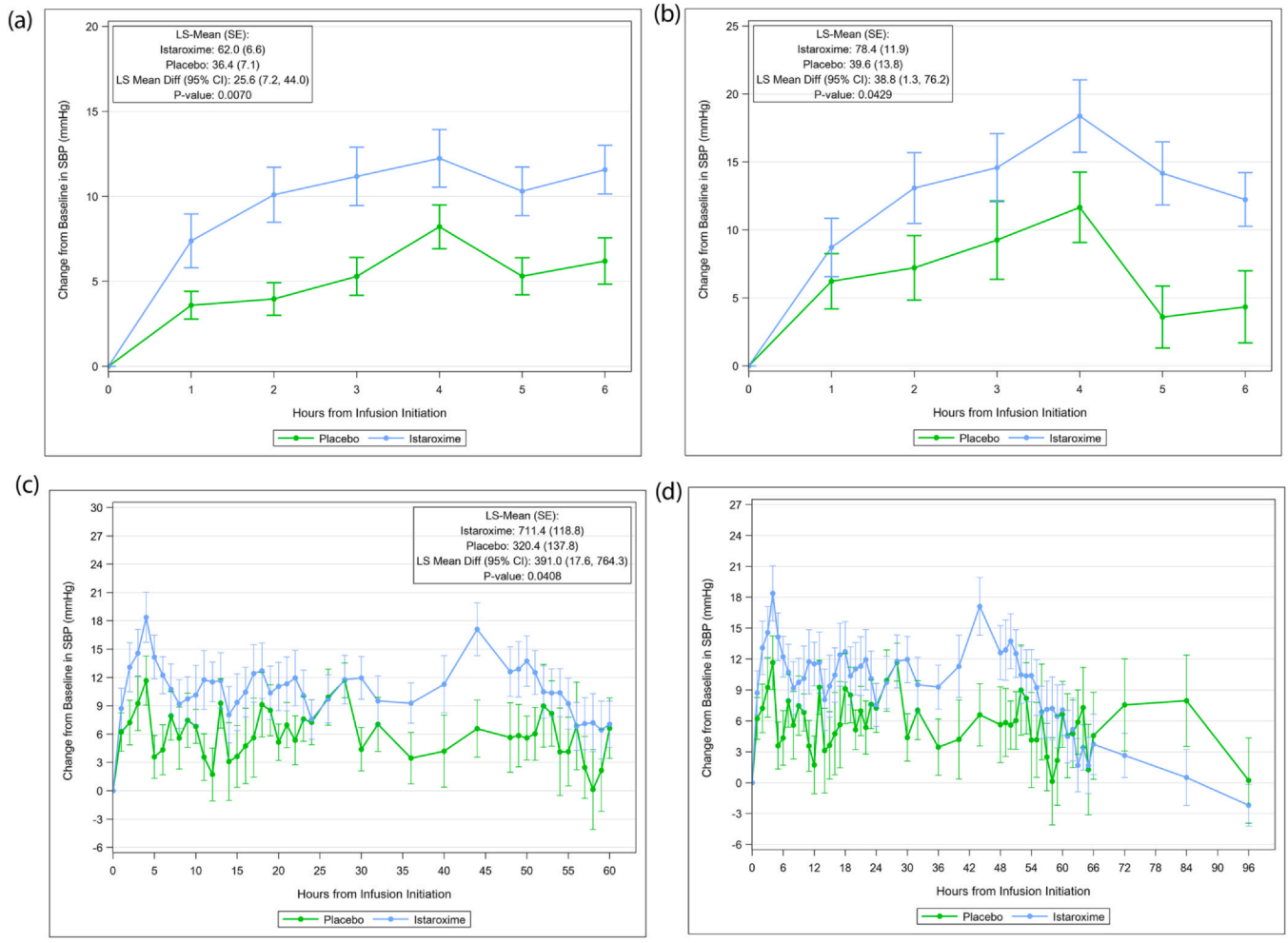

Figure 2 Changes in SBP **(a)** SEISMiC A+B AUC to 6 hours (primary endpoint), **(b)** SEISMiC B AUC to 6 hours, **(c)** SEISMiC B all specified timepoints AUC to 60 hours—imputed values, and **(d)** SEISMiC B all measurements to 96 hours—imputed values.

Effects on heart rate change are presented in Figure 3. Of note the heart rate decreased significantly in the istaroxime arm at 12 and 24 hours from randomization, and the effects became non-significant thereafter.

Effects on hemodynamic measurements

Effects of istaroxime on PCWP, CO, cardiac power output, and SvO_2 in Part B are displayed in Figure 4A-D, respectively. Effects on other hemodynamic variables are displayed in Supplemental Figures 5 and 6. Values and changes from baseline for all invasive hemodynamic parameters are provided in Supplemental Tables 2.1–2.9. The LS mean (SE) AUC for CO change through 48 hours (Supplemental Figure 6 and Supplemental Table 2.10) was 11.8 (4.02) L/min*hour in istaroxime-treated patients vs −2.7 (4.69) L/min*hour in placebo (LS mean difference 14.51, 95% CI 2.0–27.0 L/min*h, $P = 0.025$) at 24 hours. At 48 hours, the LS mean (SE) CO AUC was 25.8 (8.14) L/min*hour in the istaroxime arm vs −5.8 (9.49) L/min*hour in placebo (LS mean difference 31.55, 95% CI 6.2-56.9 L/min*h, $P = 0.017$). This translates into an approximately 0.66 L/min greater increase in CO in the istaroxime arm vs placebo on a baseline of about 3.6 L/min, that is, an improvement of about 18%.

The LS mean (SE) AUC for PCWP change through 24 hours (Supplemental Figure 6 and Supplemental Table 2.11) was −147.6 (14.10) mmHg*hour in istaroxime-treated patients vs −43.6 (15.34) mmHg*hour in placebo (LS mean difference −103.9 mmHg*hour, 95% CI −146.0-−61.8, $P < 0.0001$) at 24 hours. At 48 hours, LS mean (SE) PCWP AUCs were −336.9 (35.44) and −155.9 (38.55) mmHg*hour, respectively (LS mean difference −181.1 mmHg*h, 95% CI −286.9-−75.3, $P = 0.0017$). This difference translates into an approximately 3.8 mmHg greater decrease in PCWP in the istaroxime arm vs placebo on a baseline of about 22.5 mmHg, that is, also an improvement of about 17%.

SvO_2 tended to increase in istaroxime-treated patients and decrease in placebo during the 60-hour infusion period, with significant differences between the two treatment groups at 12, 24, and 48 hours (Figure 4). CPO increased somewhat more in the istaroxime than in the placebo group.

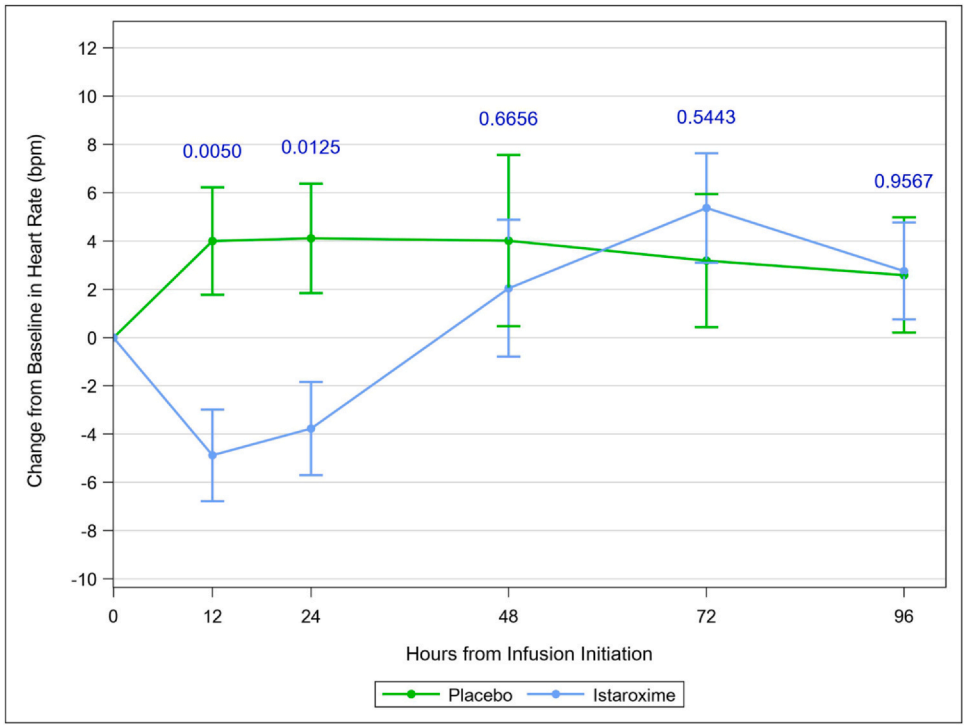

Figure 3 *Changes in Pulse at prespecified timepoints to 96 hours in SEISMiC B (Imputed values): P* values represent treatment group comparisons at individual time points, obtained from contrasts in a mixed model for repeated measures (MMRM) that included fixed effects for pooled site, baseline value, treatment group, time point, and the treatment-by-time point interaction.

Symptoms and signs of congestion, WHF events, and death

The congestion score declined in both istaroxime- and placebo-treated patients through 96 hours, with no statistically significant differences between groups (Figure 5A). NYHA class improved significantly more in the istaroxime arm to 72 hours (Figure 5B). Body weight decreased slightly more in istaroxime-than placebo-treated patients, but changes did not differ significantly between groups (Figure 5C). In the combined Parts A and B WHF, HF readmission or death occurred in three patients treated with istaroxime (at ≤ 1.0 μg/kg/min) and six patients treated with placebo through 30 days (Figure 5D). Length of stay in intensive care units and in the hospital through day 30 did not differ significantly between treatments (Supplemental Table 3).

Biomarkers

Changes in eGFR, NT-proBNP, and venous lactate levels over 96 hours in the combined Parts A and B are depicted in Figure 6A-C. Of note, eGFR improved more in the istaroxime arm at 24-72 hours, NT-proBNP increased more in the istaroxime arm at 12-72 hours, and venous lactate decreased significantly more in the istaroxime arm at 12 hours and increased more in the istaroxime arm at 96 hours. Similar changes were seen in Part B alone (Supplemental Figure 7).

Echocardiographic assessments

Due to small numbers and incomplete assessments, we report changes in echocardiographic measures only in Parts A (1.0) and B combined at 24 hours, where echocardiographic measurements were available in both study parts. Table 2 and Supplemental Tables 4.1–4.11 provide detailed echocardiographic results, including combined data from Parts A (1.0) and B, along with the number of patients assessed at each timepoint.

Guideline directed medical therapy (GDMT)

At 96 hours from randomization, more patients in the istaroxime arm were receiving GDMT. The percentage of patients on renin angiotensin system inhibitors was 68.4% in the istaroxime arm vs 45.5% in placebo. For beta blockers, the percentages were 78.9% vs 63.6%, for mineralocorticoid antagonists 84.2% vs 72.7% and for sodium-glucose cotransporter-2 inhibitors were 89.5% in the istaroxime arm vs 63.6% in the placebo arm. There was no observed difference between the percentage of optimal

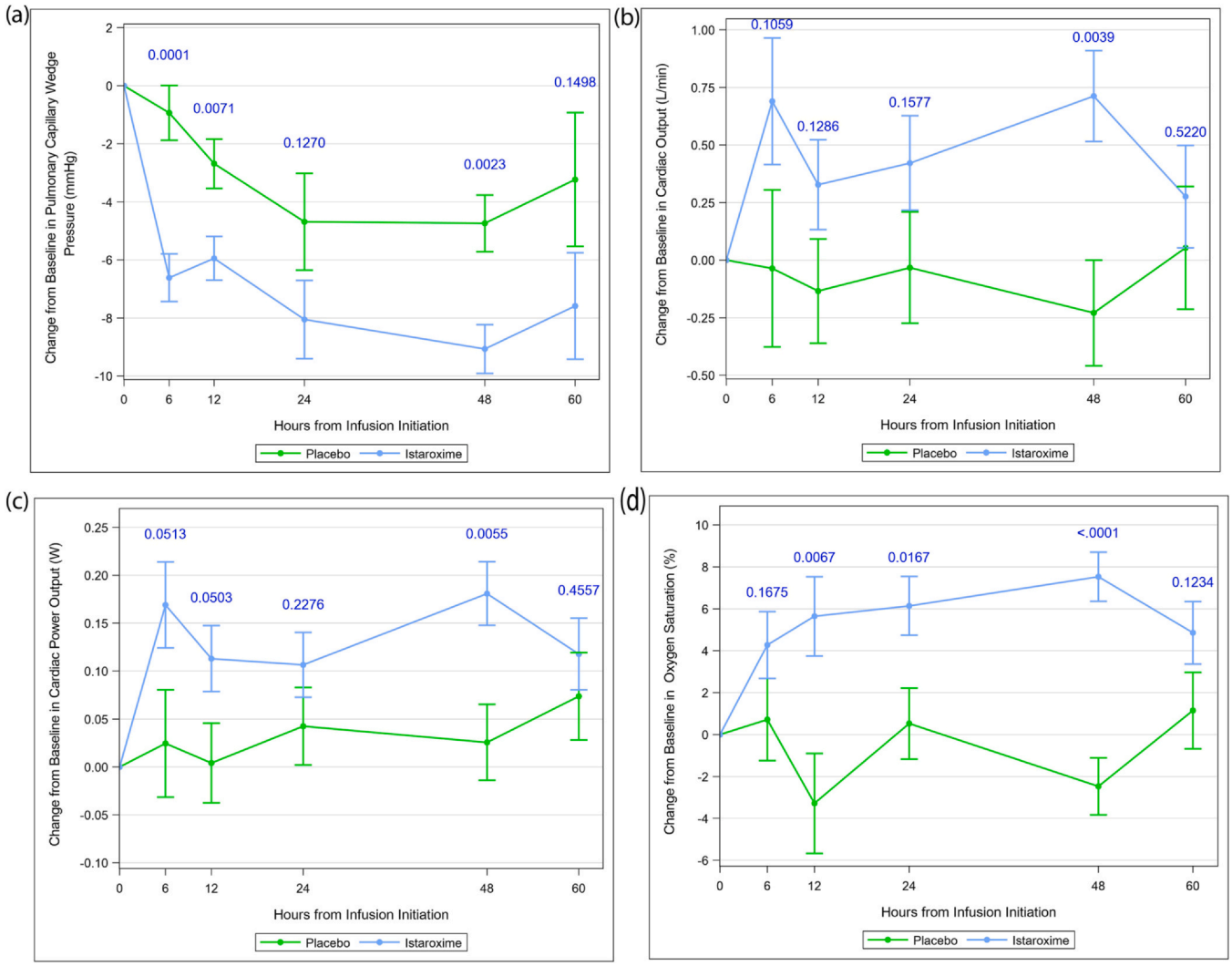

Figure 4 *Changes in hemodynamic variables to prespecified time points to 60 hours in SEISMiC B (Imputed values):* ***(A)*** *Wedge pressure,* ***(B)*** *Cardiac Output,* ***(C)*** *Cardiac Power Output, and* ***(D)*** *SVO2: P*-values represent treatment group comparisons at individual time points, obtained from contrasts in a mixed model for repeated measures (MMRM) that included fixed effects for pooled site, baseline value, treatment group, time point, and the treatment-by-time point interaction.

target dose in these medication classes (Supplemental Table 5.1).

The number of patients on loop diuretics at 96 hours was similar between the two groups, with 94.7% and 81.8% of patients on diuretics at that time in the istaroxime and placebo arms, respectively. Mean differences in furosemide equivalent dose at 96 hours were also similar (LS mean difference −2.2 mg, 95% CI −169.4-164.9, $P = 0.98$) (Supplemental Table 5.2).

Safety

There were no differences in the proportions of patients with clinically significant arrhythmias detected by centralized Holter readings through 72 hours post-infusion start by treatment arm in Part B, with 17 of 19 (89.5%) istaroxime patients and 11 of 11 (100%) placebo patients having sufficient data to be analyzed (Supplemental Table 6). There were no sustained ventricular tachycardias (VTs), ventricular fibrillation, or any other malignant ventricular tachyarrhythmias detected in either study arm.

Adverse events were reported for 15/19 (78.9%) of istaroxime-treated patients and 5/11 (45.5%) of placebo-treated patients through 30 days post-infusion start in Part B (Supplemental Table 7). Of note, two patients in the istaroxime arm had nausea and vomiting vs zero in placebo, and nine patients in the istaroxime arm had administration site pain or inflammation vs zero in placebo. Two patients in the istaroxime arm vs zero in the placebo had headaches. Serious adverse events were reported for 2 (10.5%) istaroxime-treated patients and 3 (27.3%) placebo-treated patients. Two patients in the istaroxime arm and zero in the placebo

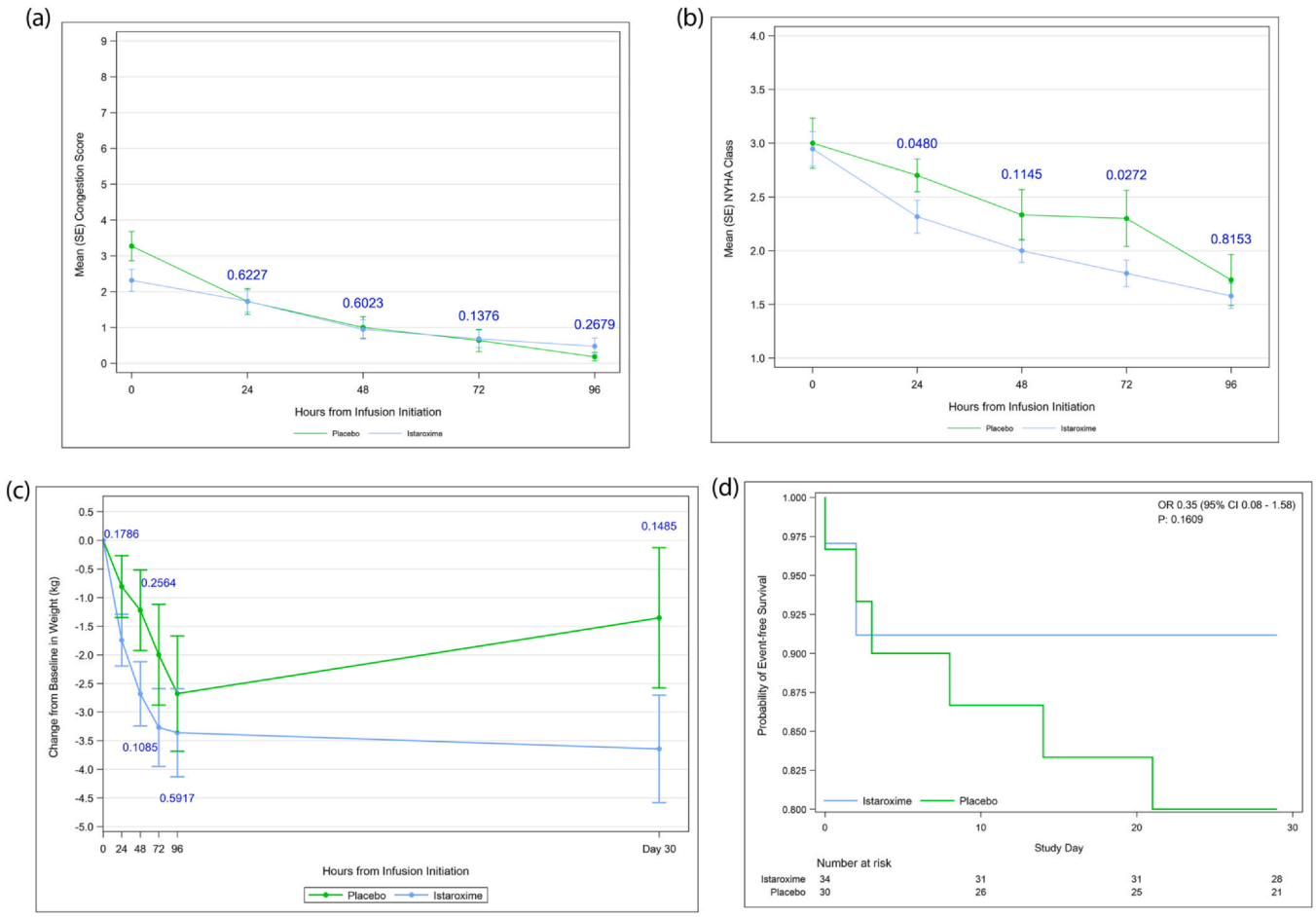

Figure 5 *Changes in markers of congestion* ***(A)*** *Congestion score to 96 hours in Part B* ***(B)*** *NYHA class to 96 hours in Part B* ***(C)*** *Weight to day 30 in Part B; and* ***(D)*** *time to WHF, HF readmission or death to day 30 in Parts A (1.0) and B combined: P-values in figures* **A**, **B**, and **C** represent treatment group comparisons at individual time points, obtained from contrasts in a mixed model for repeated measures (MMRM) that included fixed effects for pooled site, baseline value, treatment group, time point, and the treatment-by-time point interaction.

had infections. (Supplemental Table 8). No patients died through 30 days in Part B.

Other laboratory evaluations

Other laboratory data changes throughout the study are presented in Supplemental Table 9.

Discussion

The results of SEISMiC B of the effect of istaroxime administered up to 60 hours on hemodynamic assessments and of the combined SEISMiC A and B evaluation for SBP, echocardiographic assessments, clinical events, and safety suggest that istaroxime in the doses of 0.5-1.0 μg/kg/min administered for up to 60 hours can safely improve SBP while increasing CO and reducing PCWP without causing arrhythmias or increasing heart rate. This effect was associated with significant improvements in SvO_2 and kidney function as measured by eGFR, reduction in NYHA class, and numerically less WHF events or death to day 30. The effects on SVO2 and heart rate are especially large and may have significant clinical implications. Pulse tended to decrease early during the administration of istaroxime, and there were no significant arrhythmias—especially malignant ventricular arrhythmias—detected during 72 hours of Holter monitoring in the istaroxime-treated patients. Notably, the study population mirrors patients with HF-related CS as defined recently.[25] These patients were stabilized before being enrolled in the study, mostly with intravenous diuretics and some other GDMT therapies. Of HF-CS subtypes, the SEISMiC population represents ADHF-related pre-CS, that is, patients with a history of cardiac dysfunction or heart failure who develop significant deterioration. The rate of progression in this phenotype is lower than in AMI-CS, allowing a larger therapeutic

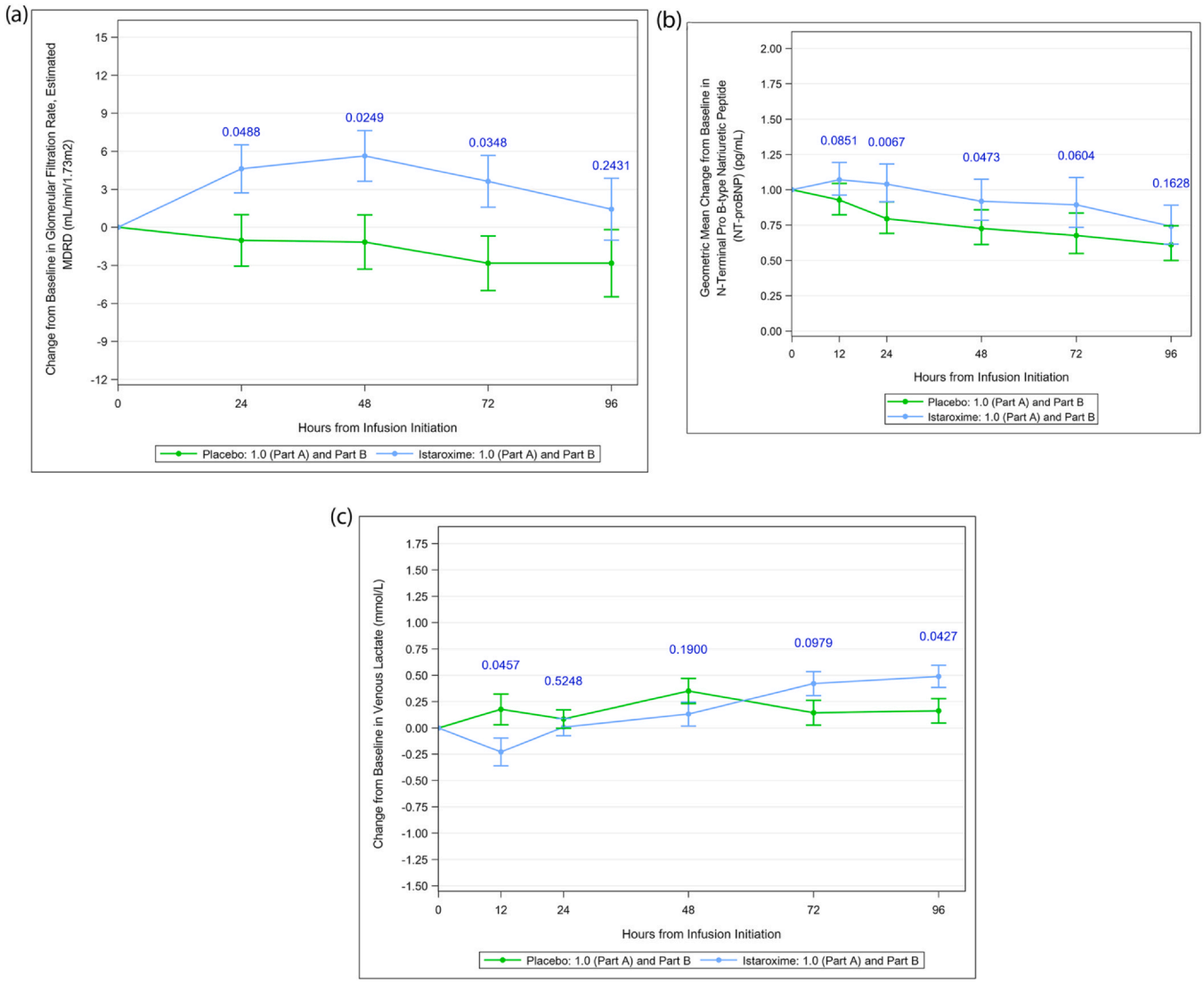

Figure 6 *Changes in* ***(A)*** *eGFR,* ***(B)*** *NTproBNP, and* ***(C)*** *Venous Lactate to 96 hours in SEISMiC* ***A*** *(1.0) and* ***B*** *combined, observed values: P*-values represent treatment group comparisons at individual time points, obtained from contrasts in a mixed model for repeated measures (MMRM) that included fixed effects for study part, baseline value, treatment group, time point, and the treatment-by-time point interaction. NTproBNP values were log transformed for analyses presented in figure **B**.

window.[26] Therefore, interventions aimed at improving BP, hemodynamic, kidney function, and symptoms of HF during this period may prove valuable in preventing progression from pre-CS to overt or worsening CS and allowing for patient stabilization and implementation of GDMT therapies. Indeed, in the SEISMiC B study, patients treated with istaroxime had higher rates of treatment with GDMT at 96 hours than patients assigned to placebo, there

Table 2 Change in Echocardiographic Measurements to Hour 24 in Parts A (1.0) and B Combined.

	Istaroxime		Placebo			
	n	LS-Mean (SE)	*n*	LS-Mean (SE)	LS-Mean Difference (95% CI)	*P* value
E/A ratio	15	−0.54 (0.19)	15	0.18 (0.19)	−0.72 (−1.25, −0.19)	0.0092
E/Ea ratio	29	−1.18 (0.88)	26	−1.42 (0.95)	0.24 (−2.37, 2.85)	0.8556
Left Atrial Volume (mL)	30	−7.92 (3.00)	25	1.90 (3.44)	−9.81 (−19.1, −0.58)	0.0378
LV End Diastolic Volume (mL)	31	−1.82 (5.97)	27	10.99 (6.61)	−12.8 (−30.9, 5.26)	0.161
LV End Systolic Volume (mL)	31	−4.51 (4.59)	27	6.02 (5.10)	−10.5 (−24.4, 3.37)	0.1347
LVEF (%)	31	1.82 (0.64)	27	0.84 (0.71)	0.98 (−0.96, 2.92)	0.3167
TAPSE (mm)	32	1.46 (0.48)	28	−0.11 (0.52)	1.57 (0.12, 3.01)	0.0344

were also numerically more patients in active then control that were on optimal doses of GDMT, and the dose of loop diuretics at 96 hours was numerically lower in active then control. These higher rates of GDMT at 96 hours may have contributed to some trends to reduced BP after study drug discontinuation.

To date, patients with acute heart failure at risk of CS and with developing CS are treated with diuretics and sometimes vasoactive/inotropic drugs or more rarely, mechanical circulatory support devices.[27,28] Milrinone or dobutamine were developed more than 40 years ago, and at the time, comprehensive studies comparing the effects, and especially the hemodynamic effects, of these drugs to placebo were not common. Therefore, our knowledge of the effects of these drugs comes from small studies where the drug effect is derived from pre-intervention comparison with on-intervention effects after a few hours or days, limiting the reliability of the data.[29–33] Taking these limitations into account, administration of these drugs leads to increases of CO and reduction of PCWP, but also a decrease in vascular resistance, lower BP, and arrhythmias with no effect or even deleterious effects on outcomes.[34,35] For levosimendan, which was developed more recently, prospective studies do exist,[36] suggesting that the effects of levosimendan are smaller than istaroxime when it comes to improvement in CO, but are similar with respect to PCWP and SvO_2. Levosimendan administration also leads to reductions in SVR and hence some BP reductions. Mechanical support devices such as the Impella microaxial left ventricular assist device were suggested to also have beneficial effects on hemodynamics[9] and outcomes.[10] These devices are rarely sued on patients with CS due to acute heart failure who are older and suffer of severe comorbidities. Furthermore, they have been shown to have significant side effects and device-related complications that may limit their efficacy.[10,37–40]

In the SEISMiC study, administration of istaroxime was associated with increased levels of natriuretic peptides during the period of istaroxime administration. The reasons for this are not clear, as the increase in NT-proBNP was not associated with worsening of congestion and was associated with numerical decrease in weight and significant improvement in NYHA class. It is possible that some effects of istaroxime on the myocardial cells lead to direct effects on natriuretic peptide secretion. This may mirror the effects of digoxin, which was previously shown to be associated with increases of natriuretic peptides.[41] Increase in natriuretic peptides may have contributed to some of the effects seen in the current study. We also observed a bidirectional effect of Istaroxime administration on serum lactate, with levels decreasing during study drug administration, reaching statistical significance at 12 hours and increasing after study drug discontinuation, reaching statistical significance at 96 hours in patients, which may represent a withdrawal effect. Alternatively, it may represent a metabolic effect of istaroxime unrelated to its hemodynamic effects. These hypotheses require further study.

Regarding safety, there were more access site inflammatory reactions in the active group than in the control group. Additionally, there were two adverse events of nausea and vomiting in the active group and none in the control group, as well as two serious adverse events of infection in the active group and none in the control group.

Limitations

The SEISMiC study is a small exploratory phase 2 study. The results need to be replicated in larger studies, including patients with more severe CS and with more clinically significant outcomes. Such studies are currently in progress. The study was not powered to assess safety endpoints, and hence the safety results should be interpreted cautiously. Finally, there is some bias in the population studied due to the limitation of inclusion to patients who were not perceived to be in need for rescue therapy within 6 hours of enrollment.

Conclusions

Istaroxime was shown in the SEISMiC study in patients with ADHF-related pre-CS to simultaneously improve BP and CO and reduce in PCWP while not increasing pulse or leading to excess arrhythmias.

Disclosure statement

The SEISMiC study is sponsored by Windtree Therapeutics, Inc.

Conflicts of Interest statement

MM received personal fees of minimal amounts in the last three years from Amgen, Livanova, and Vifor pharma as member of Executive or Data Monitoring Committees of sponsored clinical trials; from Astra-Zeneca, Abbott vascular, Bayer, Boheringer Ingelhelm, and Edwards Therapeutics for participation to advisory boards and/or speeches at sponsored meetings. MP received personal fees from Abbott Vascular, AstraZeneca, Boehringer Ingelheim, Novartis, Roche Diagnostics, and Vifor Pharma. OC is a member of the Boehringer Ingelheim Advisory Board. BD, GC, CE, MN, MB, and KT are employees of Momentum Research, which has received grants for research from the Heart Initiative, Corteria, Windtree, Echosens, and 4teen4. GF reports lecture fees and/and or advisor and/or trial committee membership from Bayer, Boehringer Ingelheim, Servier, Novartis, Impulse Dynamics, Vifor, Medtronic, Cardior, and Novo Nordisk; Research Grants from the European Union. AM reports personal fees from Orion, Roche, Adrenomed and Fire 1, and grants and personal fees from 4TEEN4, Abbott, Roche, and Sphyngotec. 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.

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Appendix A. Supporting Information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.healun.2025.05.013.

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