



Windtree Therapeutics Investor Presentation

October 1, 2024

Nasdaq: WINT



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Windtree Investment Highlights



- ✓ Biopharmaceutical company focused on cardiovascular and oncology treatments intended to address markets with significant unmet need (NASDAQ: WINT)
- ✓ First in class, novel asset istaroxime has demonstrated positive efficacy and an attractive profile in four Phase 2 global studies, highlighted by improvements in cardiac function and increases in blood pressure with favorable renal and arrhythmias profile
- ✓ Istaroxime is in Phase 2b clinical development for cardiogenic shock (CS) and acute heart failure; platform also includes next generation oral, SERCA2a activators in preclinical development
- ✓ Positive top line results from istaroxime Phase 2b SEISMic Part B Study in CS reported September 2024 with next clinical milestone planned for late Q1 '25 – in the progress toward Phase 3 readiness
- ✓ Cardiogenic shock is an estimated \$1.25B global market where patients have high mortality, morbidity and costs. It represents a significant opportunity for istaroxime because currently available drugs have undesirable side effects and can result in poor outcomes and there is a lack of competition in development or active competition in the market
- ✓ Global and regional license deals are in place with Windtree in active discussions on potential additional global license for cardiovascular assets
- ✓ Newly acquired first in class, novel, protein kinase C iota inhibitor oncology platform with both topical and oral formulations creates significant opportunity that we plan to advance this year
- ✓ Lean, capital efficient operation led by a highly experienced management team

Multi-Asset / Indication Pipeline with Several Near-Term Milestones

Product Candidates	Indication	Phase	Development Status / Plans
Istaroxime (SERCA2a activator/ Na/K ATPase inhibitor)	Cardiogenic Shock	Phase 2b	<ul style="list-style-type: none"> • Positive Phase 2b studies • Executing small follow-on studies intended to transition to Phase 3
Istaroxime	Acute Heart Failure	Phase 2b	<ul style="list-style-type: none"> • Positive Phase 2a and 2b data • Greater China regional license with Lee's Pharma who is advancing and paying for Phase 3 AHF program in territory
SERCA2a Activators (oral)	Chronic Heart Failure, including potentially HFpEF	Preclinical	<ul style="list-style-type: none"> • Chronic and Acute Heart Failure • Target for collaboration/partnership
aPKCi inhibitor (topical and oral)	Cutaneous and systemic treatment in broad and/or rare malignant diseases	Preclinical	<ul style="list-style-type: none"> • IND enabling studies
Rostafuroxin	Treatment Resistant Hypertension – Genotypically identified patients	Phase 2b	<ul style="list-style-type: none"> • Phase 2 data in hypertension • Company holding development to out-license and reposition for the attractive and large Resistant Hypertension market
KL4 Surfactant and AEROSURF	KL4 surfactant Drug/Device Tx for RDS and potential other applications	Phase 2b	<ul style="list-style-type: none"> • Global out-license in place • Partner responsible for all costs of development

Positive Istaroxime Phase 2 Studies Demonstrated:



Cardiac Function Improved

- Significant increases in cardiac output
- Significant increase in stroke volume (amount of blood pumped with each heartbeat)
- Lowered cardiac filling pressures



Increase in Systolic Blood Pressure



Increase or Preserve Renal Function (eGFR)



Decrease in Heart Rate

Favorable Heart Rhythm Profile Observed

- No increase in clinically significant arrhythmias or ventricular tachycardia

**Fast Track Approval for Acute Heart Failure and
Potential Favorable Pathway for Cardiogenic Shock**



Istaroxime

Cardiogenic Shock

Potential to transform the standard of care for critical patients

Cardiogenic Shock - *A Critical Condition Caused by a Failing Heart*

A severe presentation of heart failure characterized by **low blood pressure and inadequate blood flow to vital organs (hypoperfusion)** accompanied by congestion and high filling pressures of the heart. It **requires very urgent treatment.**



- Most often requires pharmacological or mechanical intervention with key clinical objective to increase SBP to >90mmHg and improve tissue perfusion
- Cardiogenic shock patients typically require hospital intensive care and consume significant hospital resources
- High mortality (~20-30%) and substantial morbidity in survivors¹
- US + EU markets represent an ~\$1.0B market potential² with high unmet need
- Potential for relatively faster and less expensive developmental and regulatory pathway

1) Burgos, JSCAI (1) 2021Kolte D, American Heart Association; 2014 Jan 13; (rates associated with classic, stage C shock)

2) Estimates from claims data and epi data September 2021, multiplied by assumed various regional prices

What Would the Ideal Treatment for Cardiogenic Shock due to Heart Failure Look Like?

- ✓ Improves systolic and diastolic cardiac function--the root cause of cardiogenic shock
- ✓ Improves blood pressure and organ perfusion--the main problem in cardiogenic shock
- ✓ Avoids harming the kidneys
- ✓ Does not increase heart rate or increase myocardial oxygen demand or energy requirements of the heart
- ✓ Does not increase the risk for cardiac arrhythmias
- ✓ Contributes to effective diuresis and resolving fluid overload in lungs and body
- ✓ Rapid onset of action with a predictable effect that can be titrated to individual patient needs



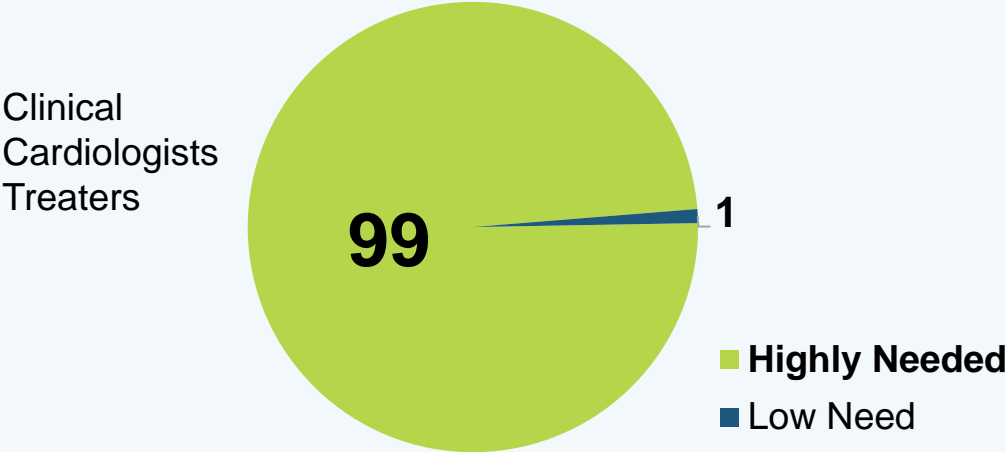
Significant Unmet Need and Reported Desire for Istaroxime

No current satisfactory pharmacological intervention to reverse the condition

- Available therapies have unwanted side effects such as risk for arrhythmias, decreasing blood pressure, renal dysfunction and even increases in mortality that limit their usefulness and position them as “rescue medicines”

Market research shows need and enthusiasm for istaroxime profile

100 U.S. Cardiologists questioned on degree of **unmet need for new innovative pharmacologic treatments for ECS¹**

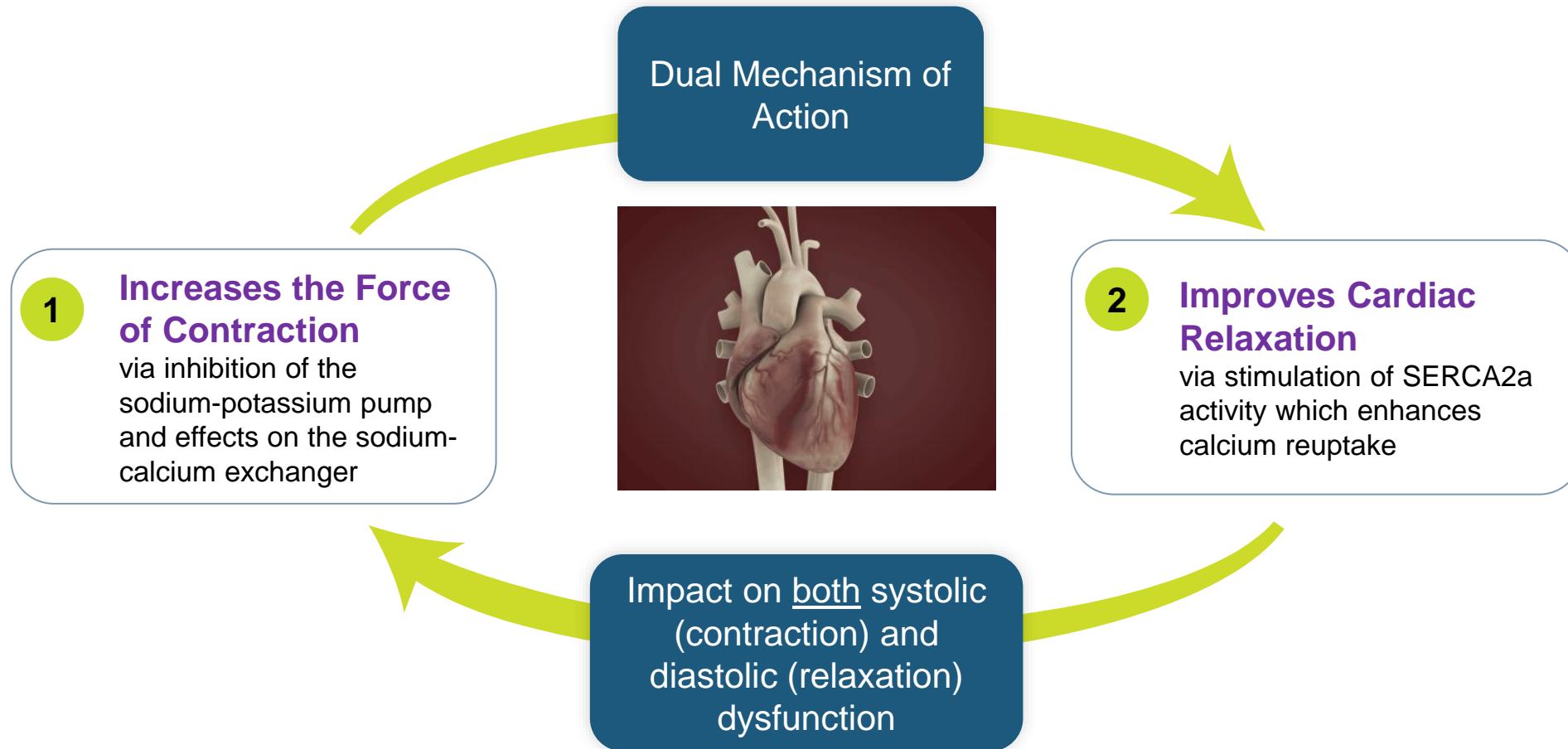


✓ **84%** of the cardiologists responded they would be **likely to extremely likely to use** istaroxime for early cardiogenic shock patients

✓ Majority responded they would position utilization before use of other existing classes of therapies such as inotropes and vasopressors

Istaroxime – Novel First-in-Class Therapy

Novel intravenous agent designed to improve systolic contraction and diastolic relaxation of the heart



SEISMic Early Cardiogenic Shock Studies

SEISMic Part A



60 patients in early cardiogenic shock (SBP 75-90 mmHg) with AHF



Study drug was infused for **24 hours** in a 1:1 randomization to placebo or istaroxime. Two istaroxime target doses were evaluated, 1.5 µg/kg/min and 1.0 µg/kg/min



Primary endpoint was SBP AUC at 6 hours comparing istaroxime to placebo

Secondary measures included: echocardiology measures of cardiac function, renal function, various safety and tolerability measures



Positive Results

SEISMic Part B

30 patients in early cardiogenic shock (SBP 70-100 mmHg) with AHF

Study drug was infused for **up to 60 hours** in a 2:1 randomization:

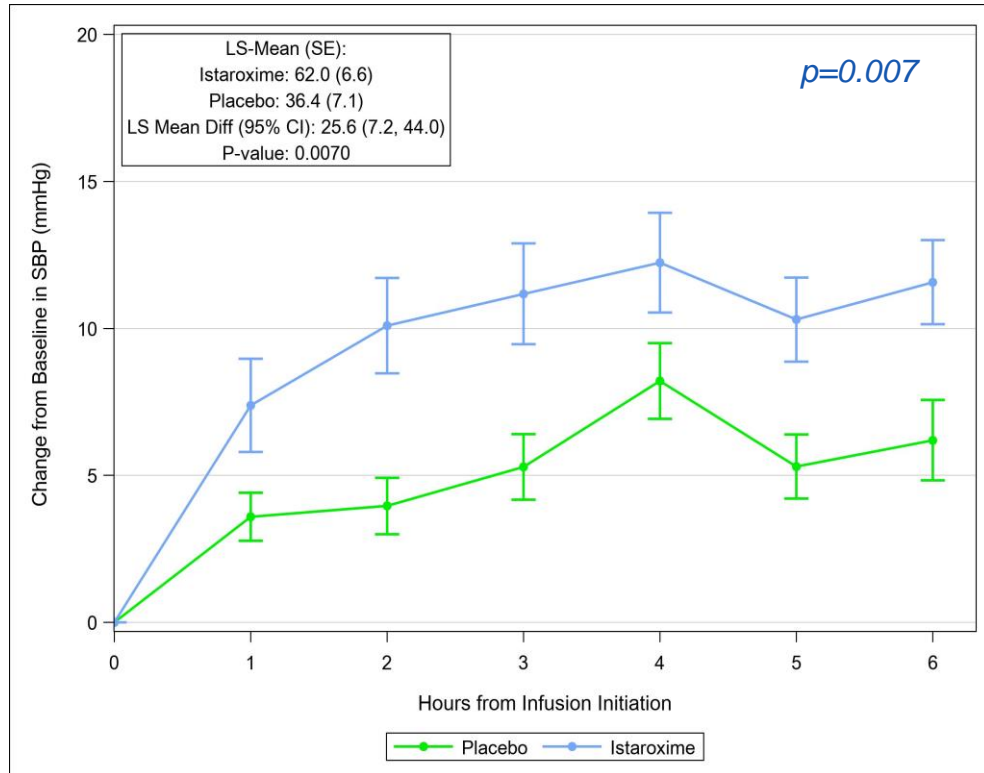
- Ista 1.0/0.5/0.25 µg/kg/min for 6/42/12 hours
- Ista 0.5 µg/kg/min 48 hrs, then placebo for 12 hrs
- Placebo for 60 hours

Primary endpoint was SBP AUC over 6 hours comparing istaroxime Part A and B to placebo

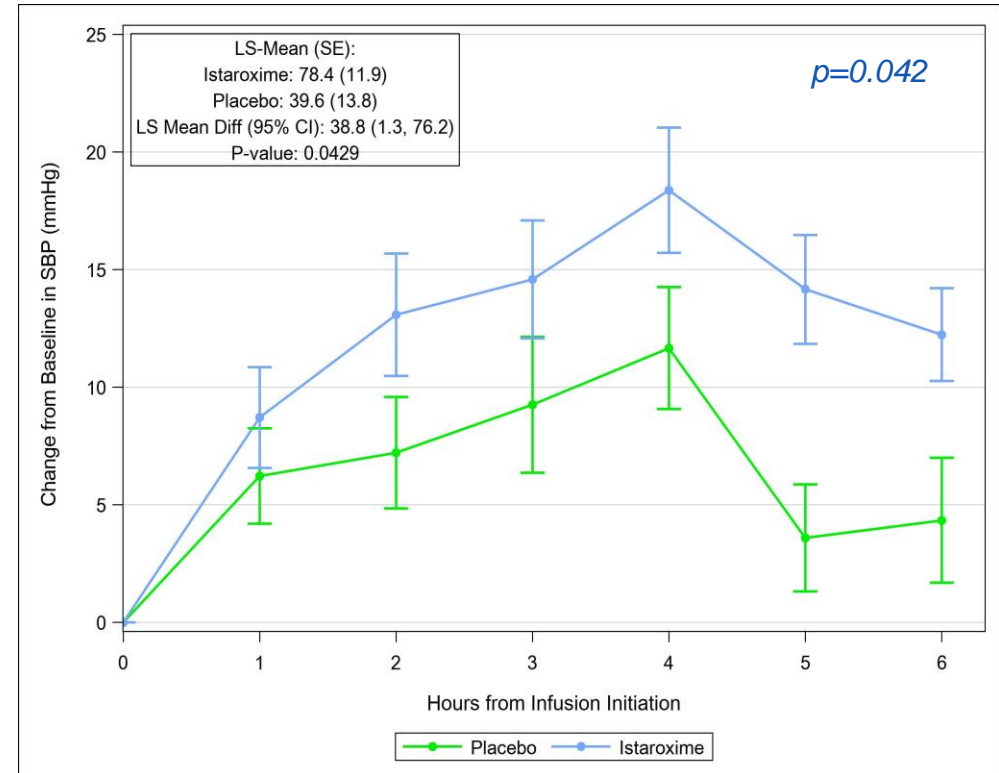
Secondary measures included SBP AUC in Part B alone, pulmonary capillary wedge pressure, echocardiography measures of cardiac function, renal function, safety and tolerability

Significant Improvement on the Primary Endpoint SBP AUC 6 hours in SEISMic and Part B Alone

SEISMic A+B

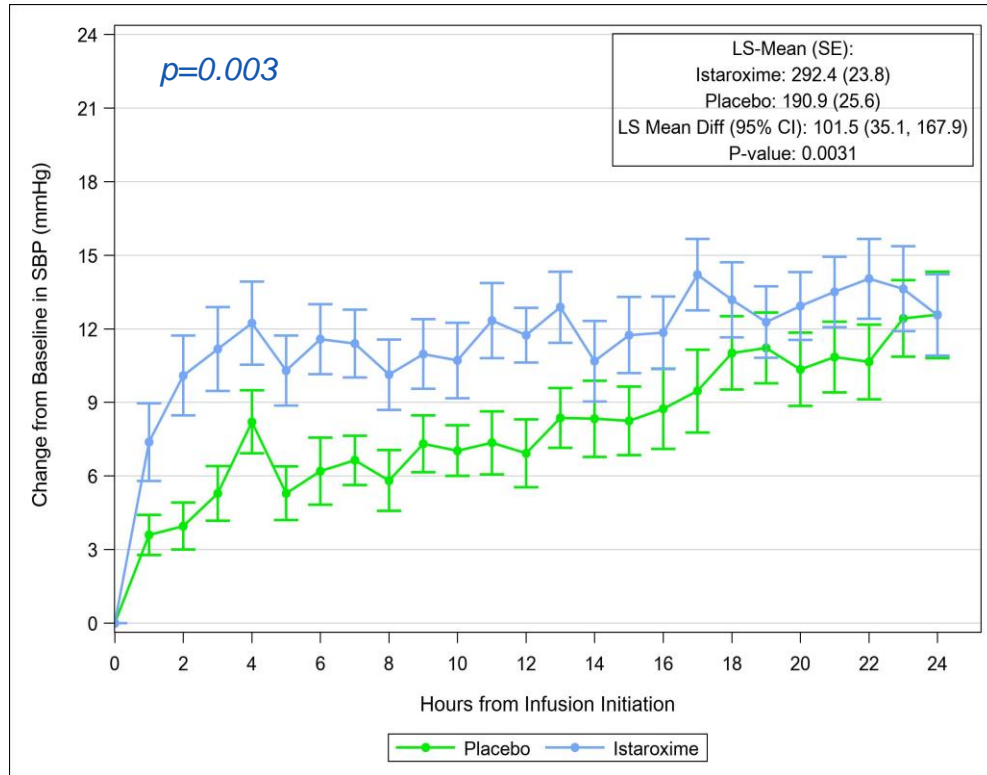


SEISMic B

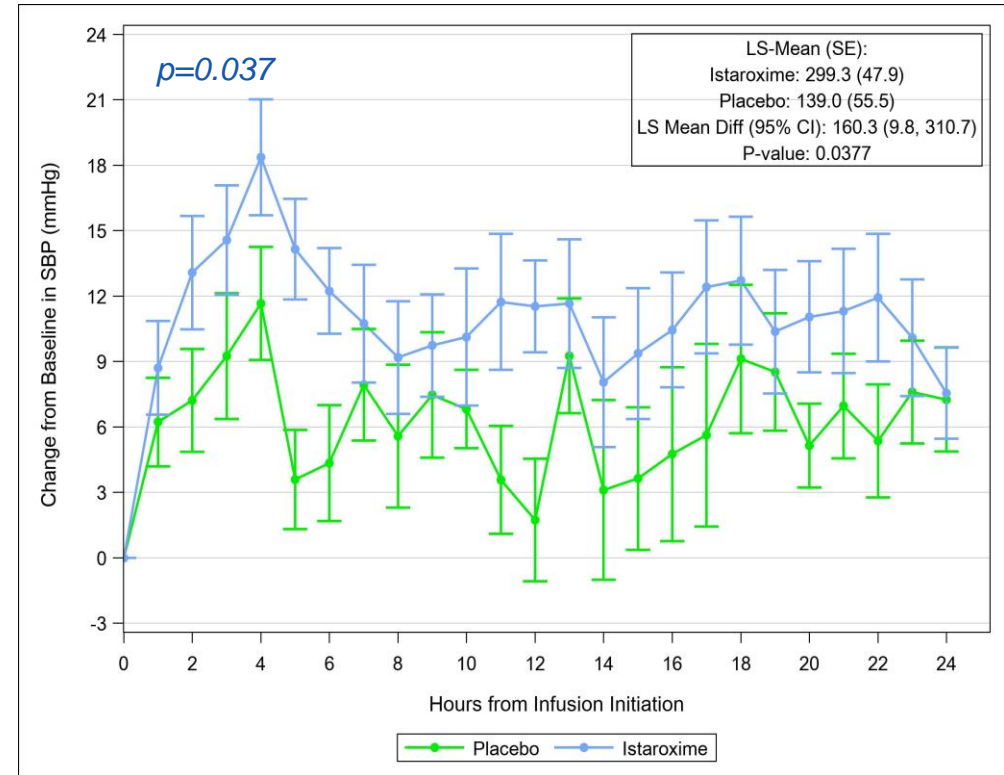


Significant Improvement Persisted with SBP AUC 24 hours

SEISMic A+B

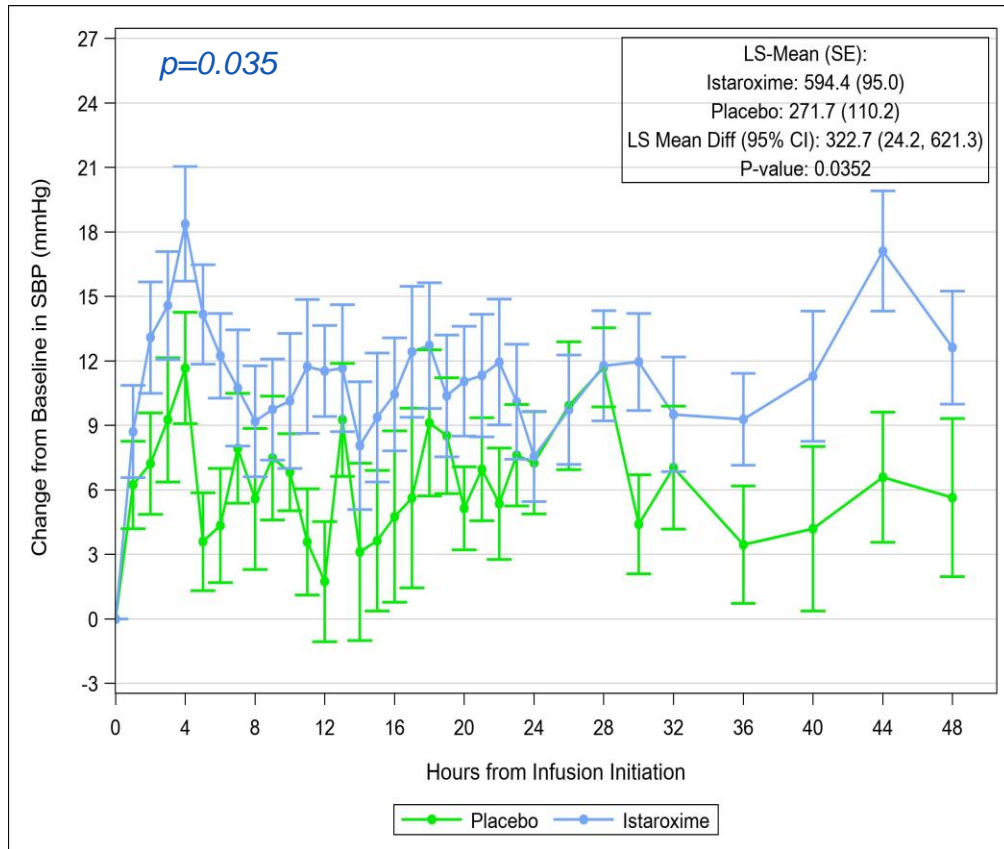


SEISMic B

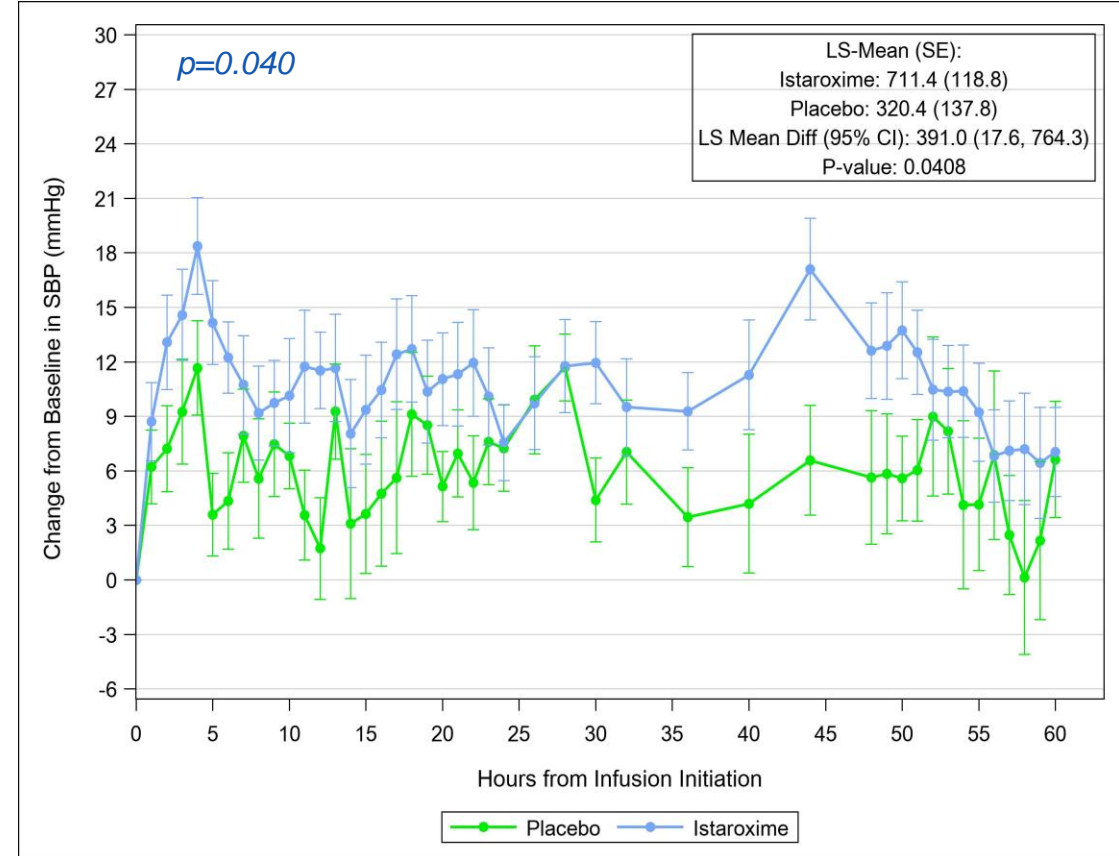


Significant SBP Increase AUC 48 and 60 hours – SEISMic B

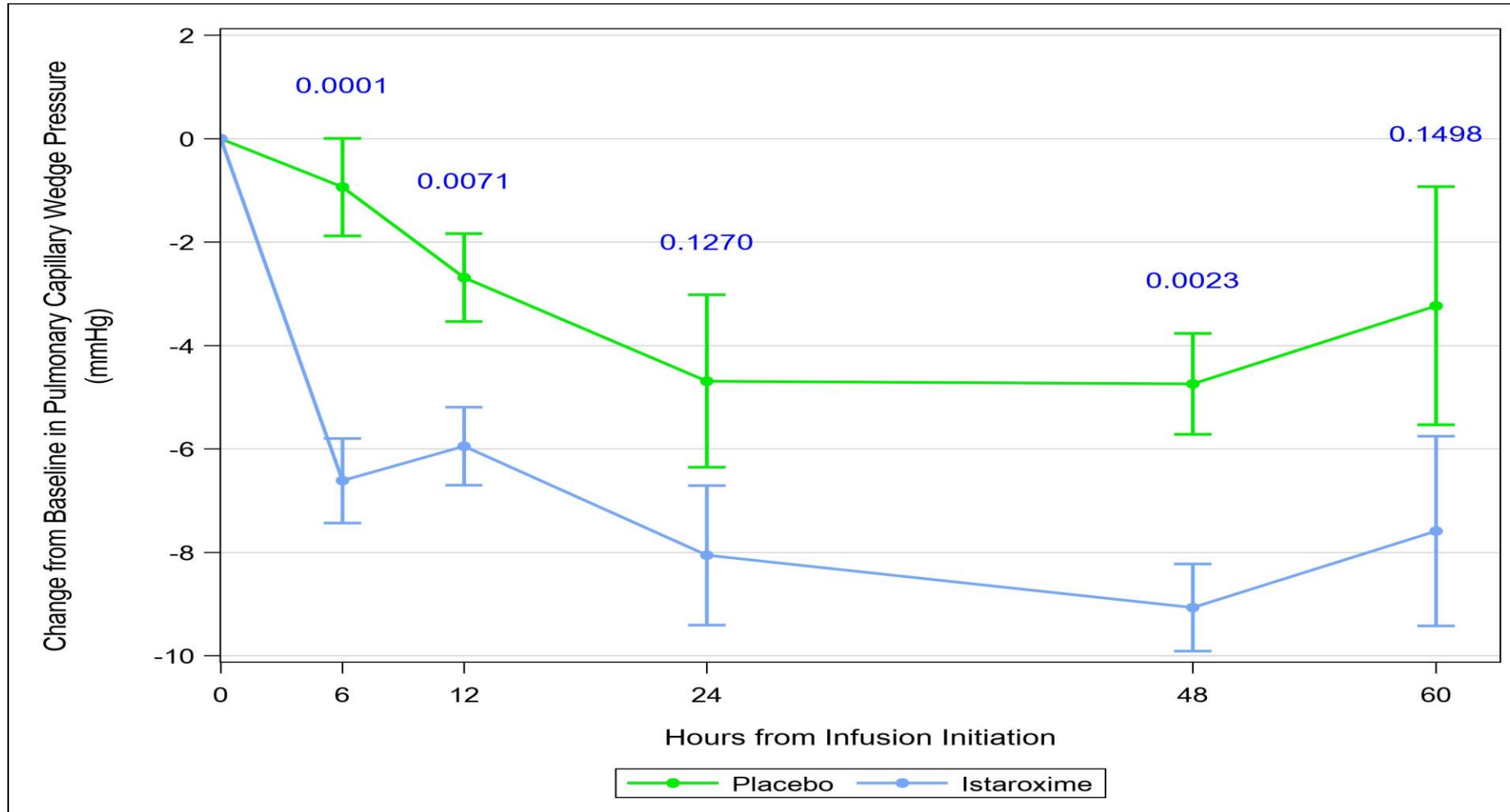
SBP AUC to 48 hours



SBP AUC to 60 Hours

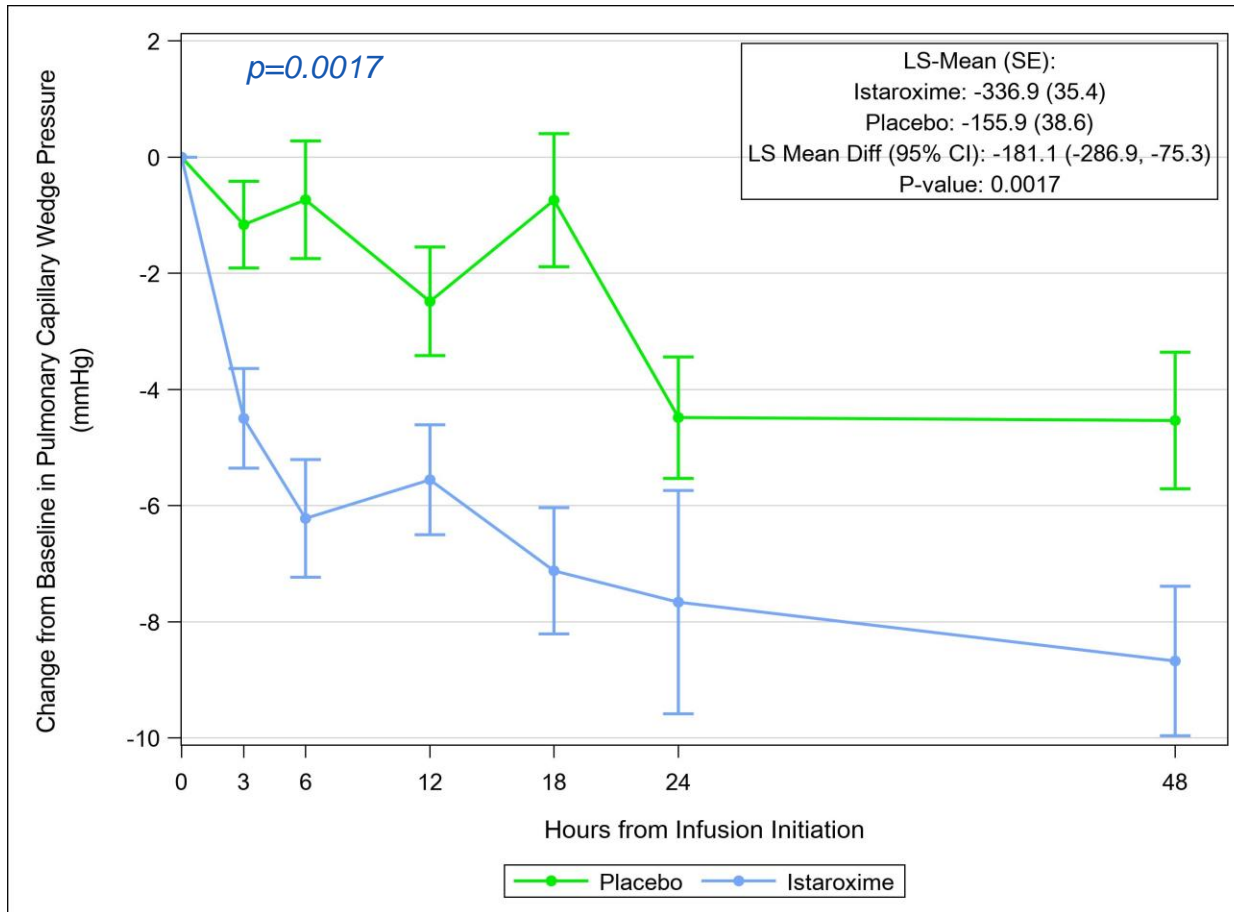


Changes in PCWP (Wedge Pressure) in SEISMIC B

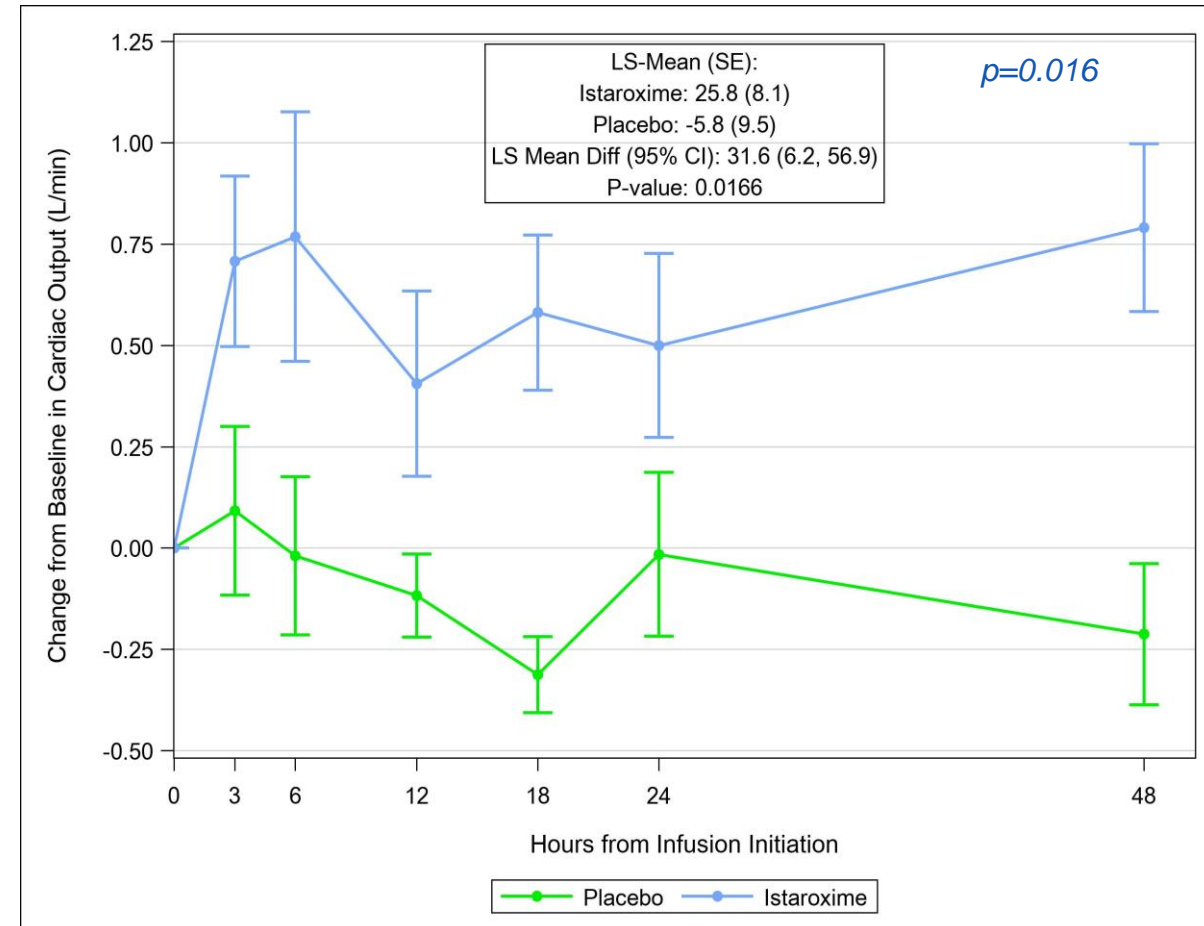


Significant Improvements in Cardiac Function Measured by Wedge Pressure and Cardiac Output AUCs to 48 hours in SEISMic B

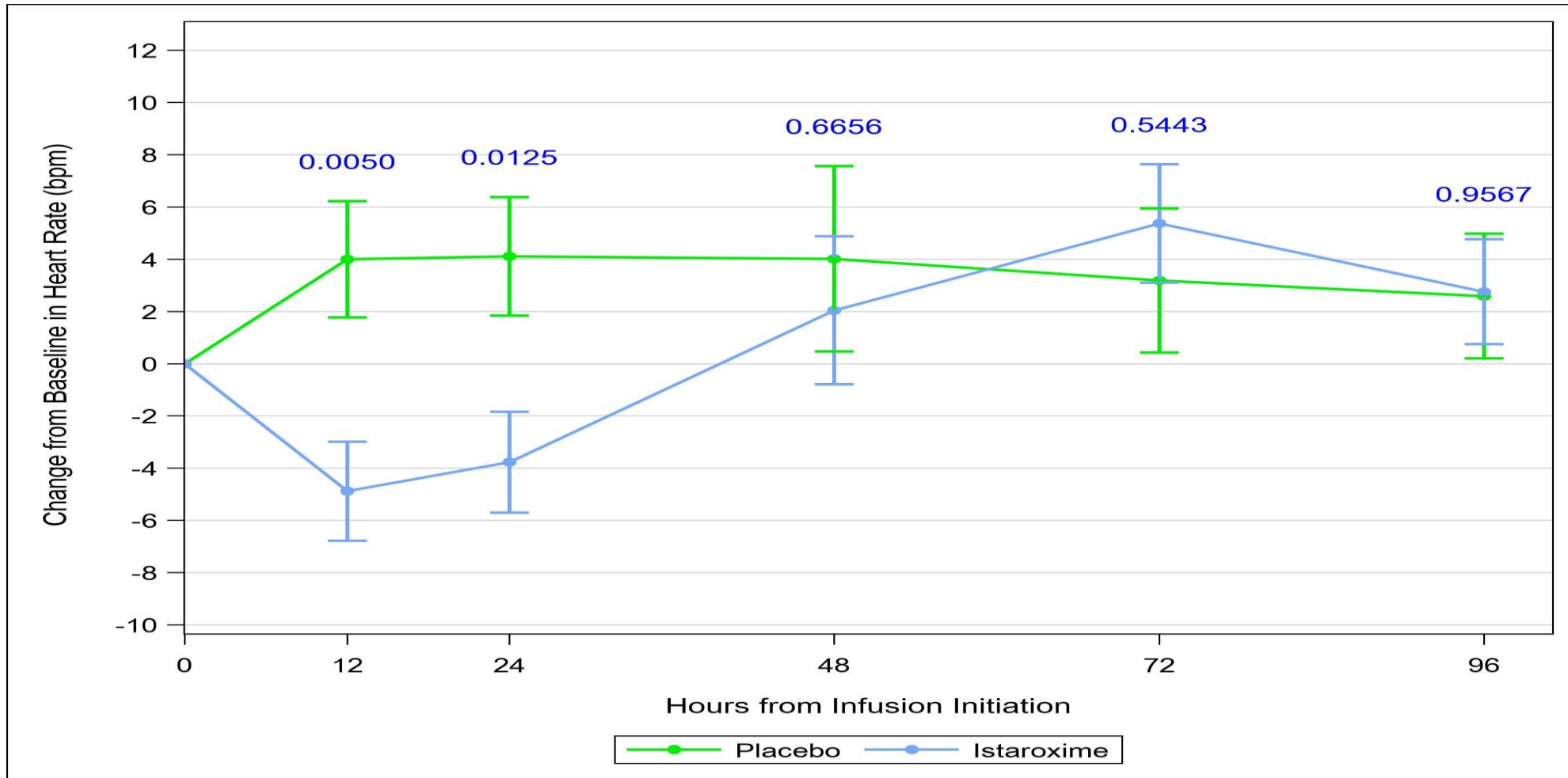
Wedge Pressure



Cardiac Output

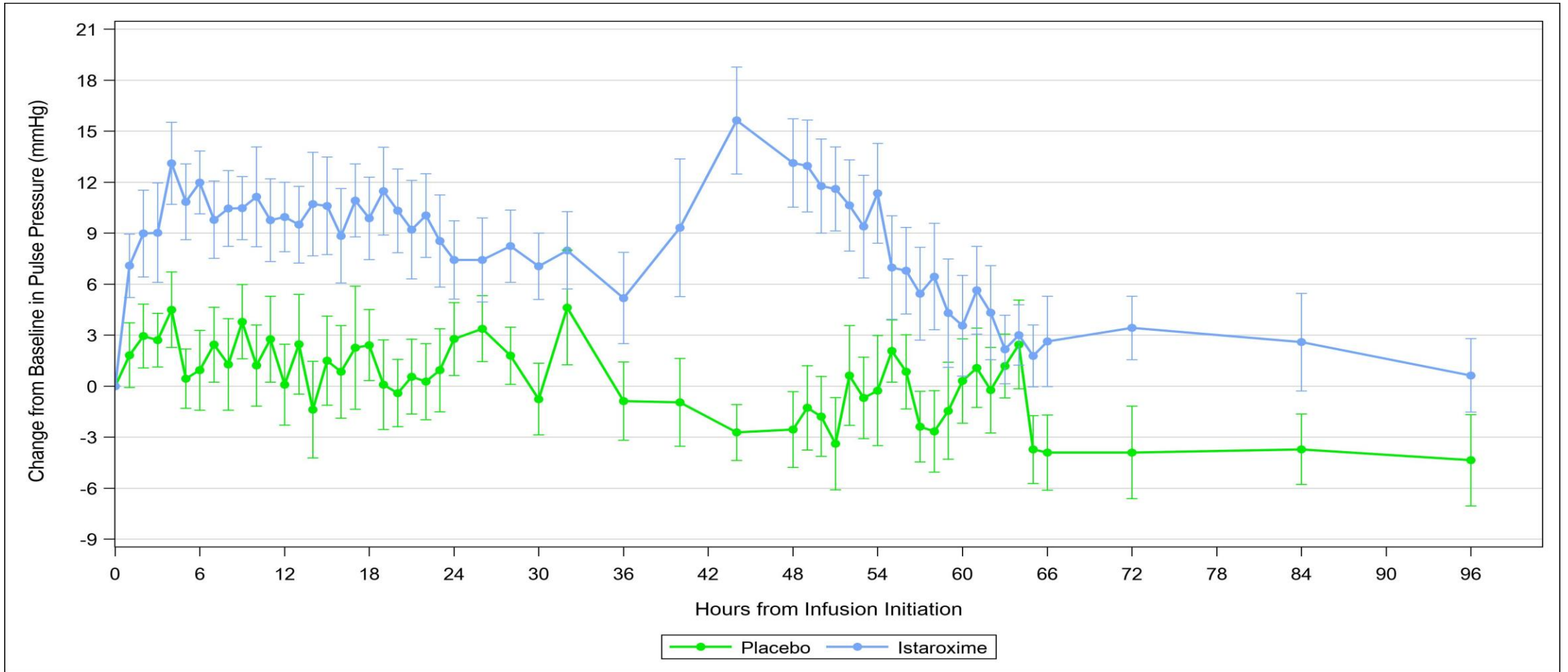


Changes in Heart Rate to 96 hours in SEISMIC B

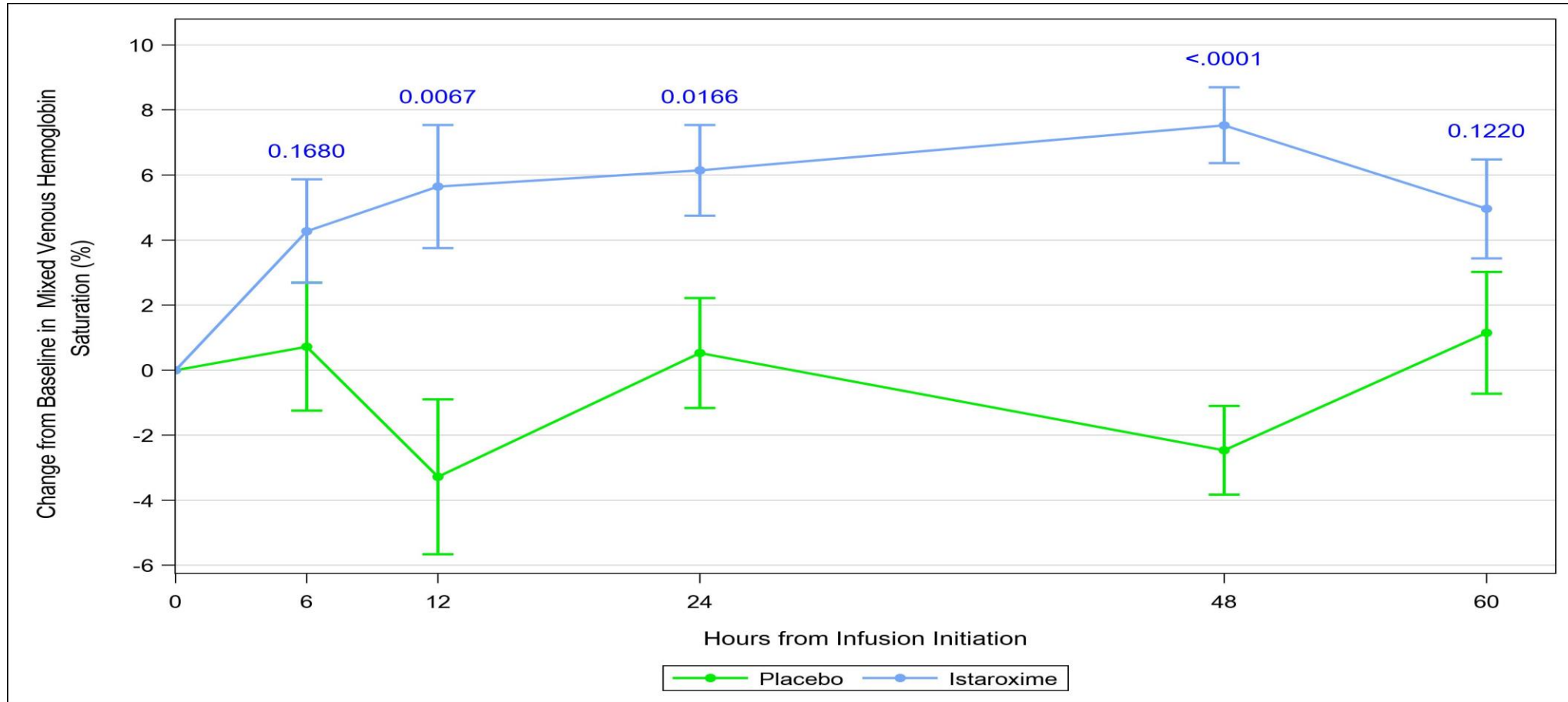


Improvements in Pulse Pressure to 96 hours - SEISMic B

Post-hoc analysis

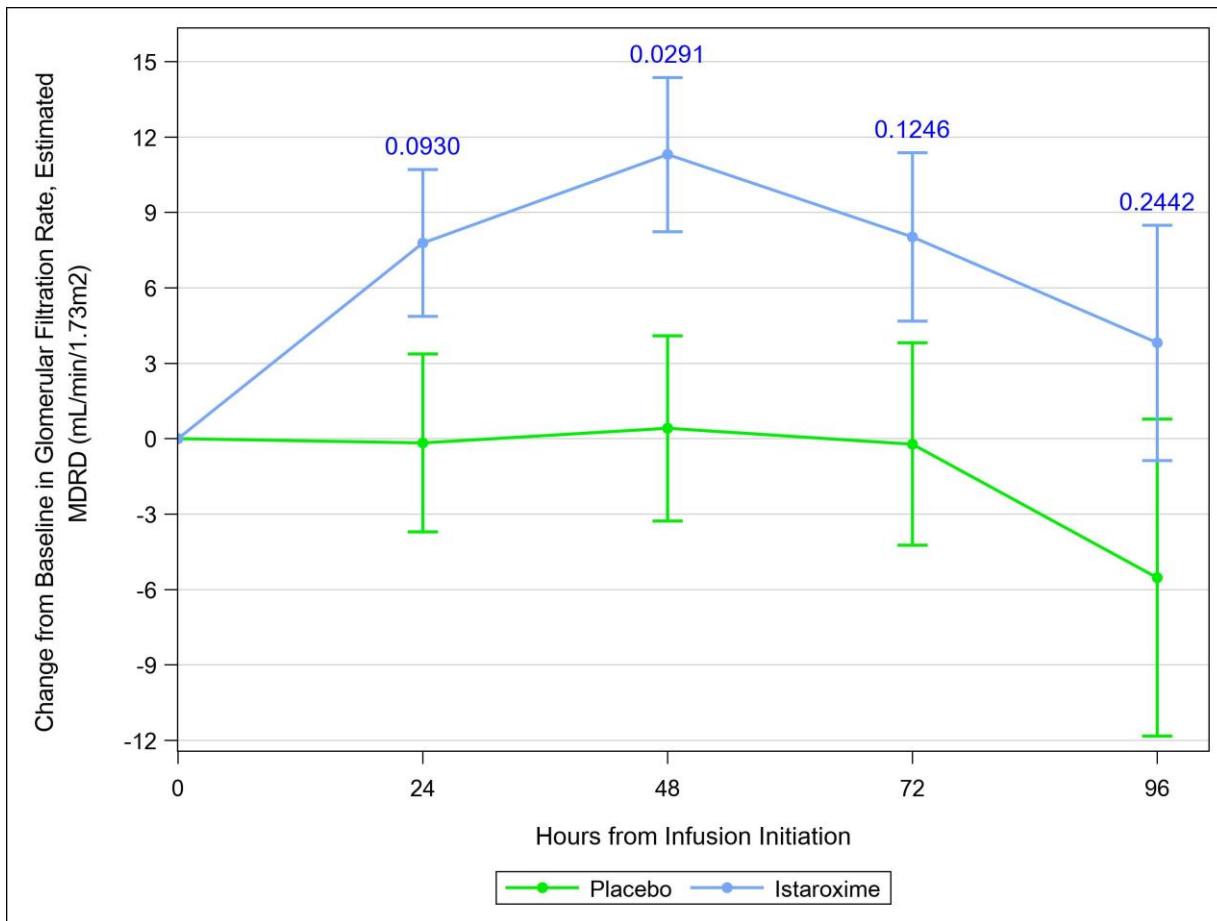


Mixed Venous Oxygen Saturation (SVO2), an Assessment of Organ Perfusion, was Significantly Improved by 12 Hours and Persisted

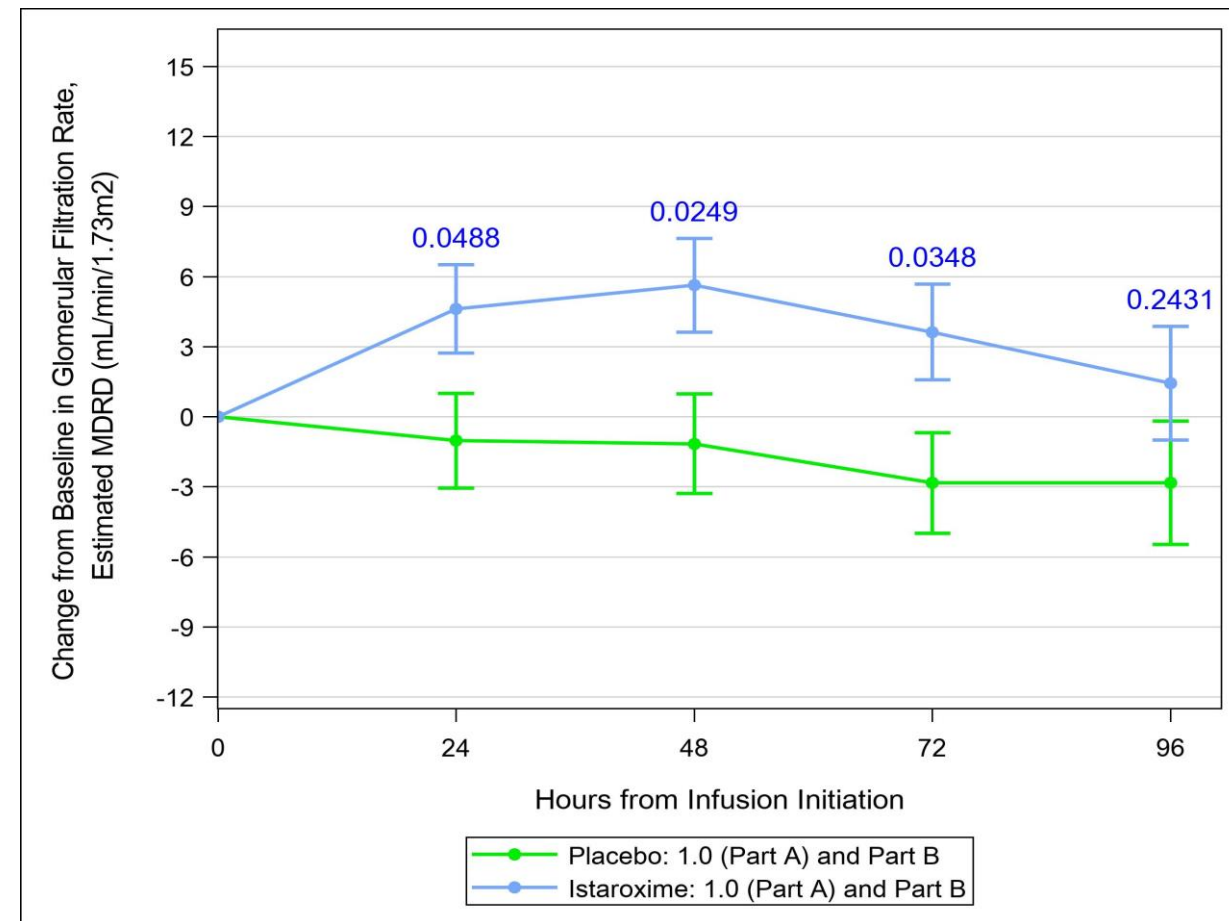


Positive Profile in Renal Function Measured by eGFR

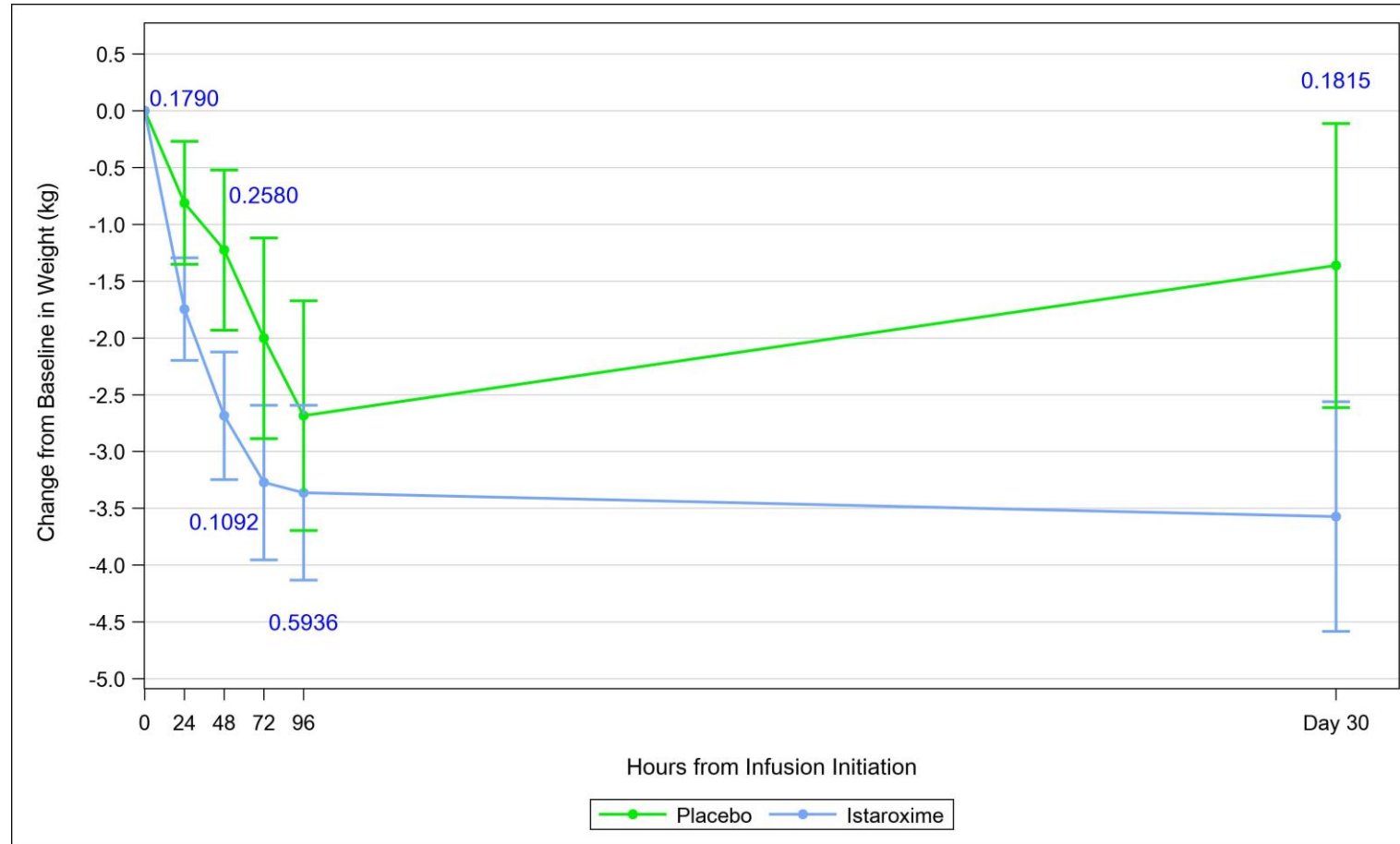
SEISMic B



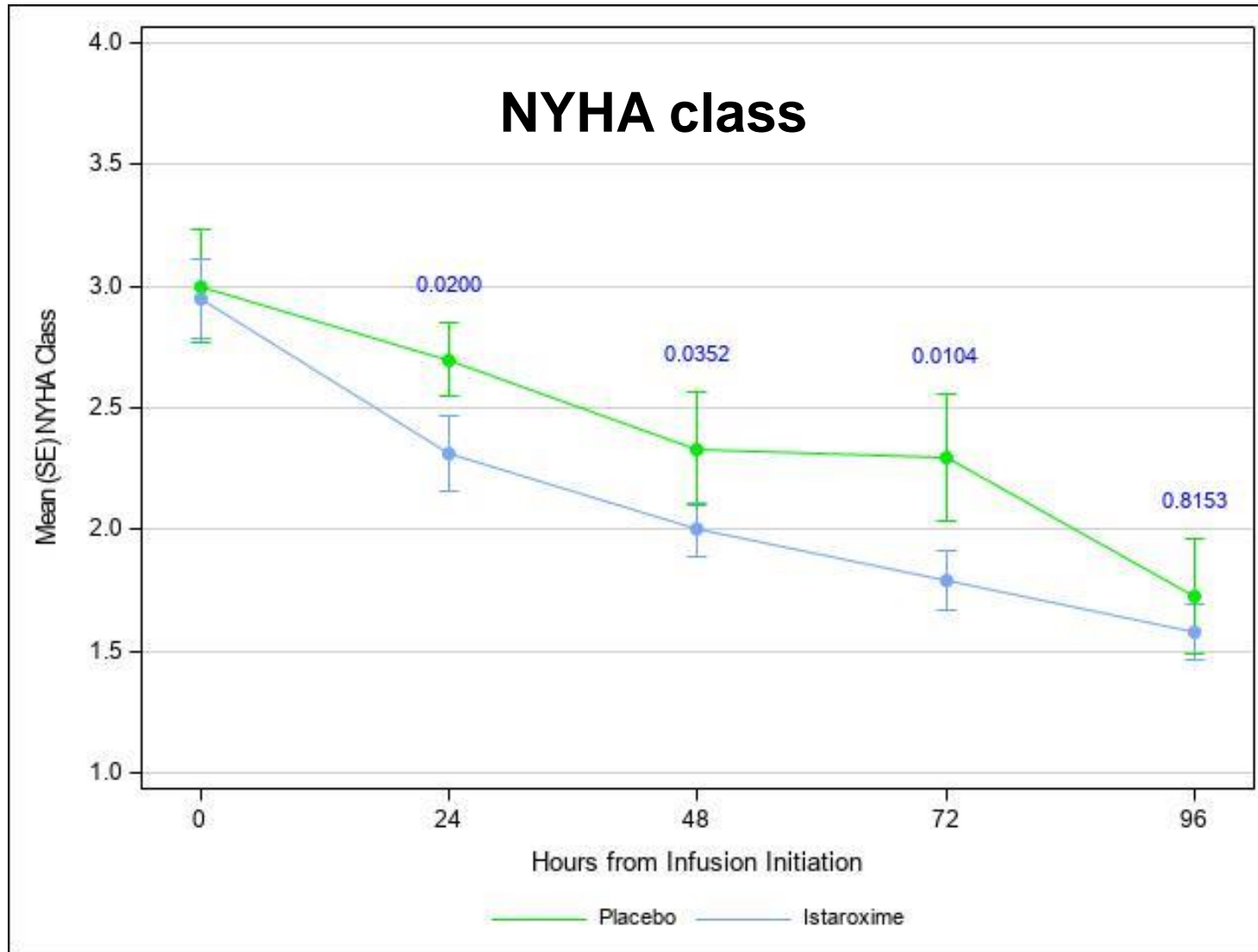
SEISMic A + SEISMic B pts. Pts. treated with ≤ 1.0 mcg/kg/min (61 Pts.)



Reductions in Weight in SEISMic B

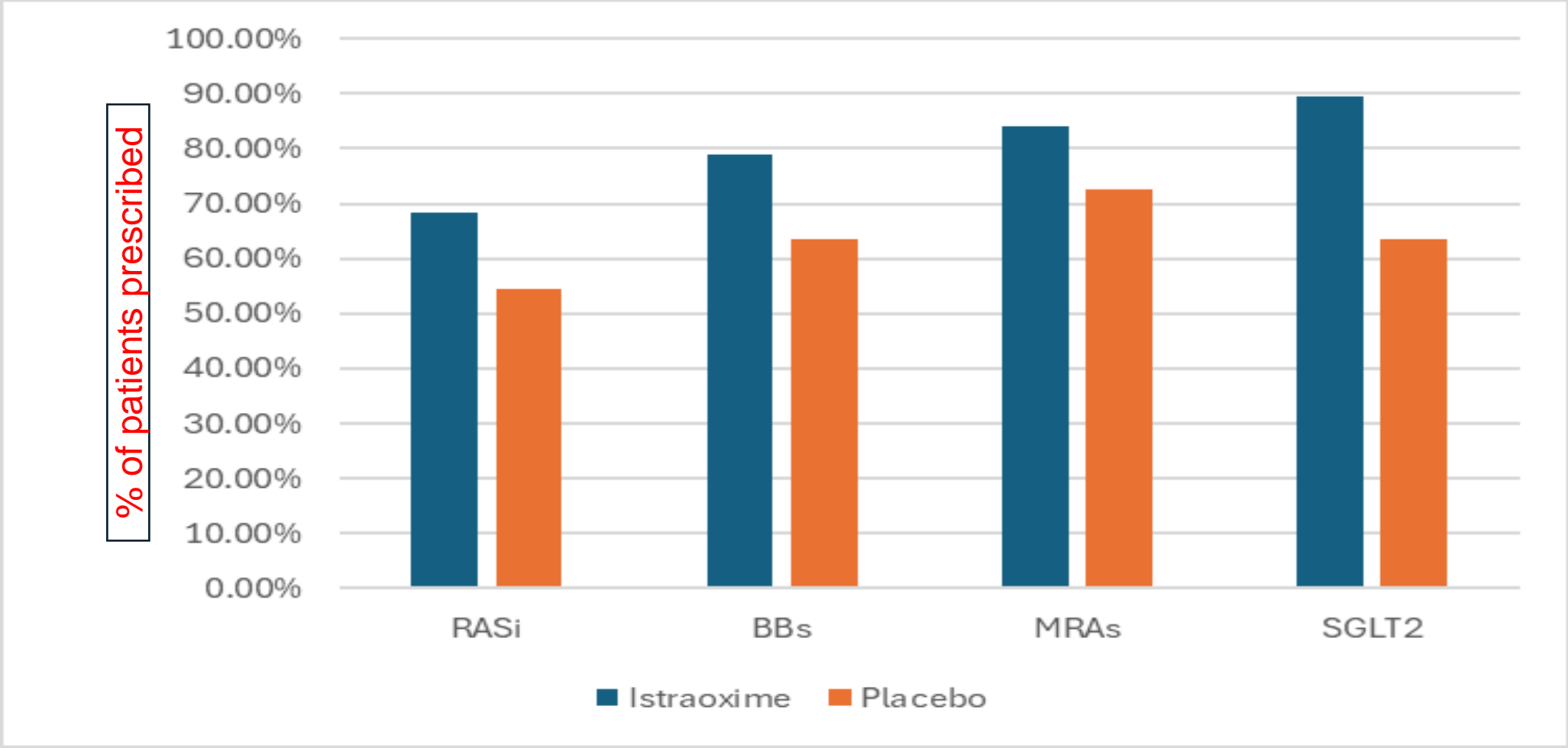


Symptoms and Signs of Congestion Improved with both Placebo and Istaroxime. Heart Failure Severity by NYHA Class Improved Significantly with Istaroxime Treatments



P-values for win odds adjusted for baseline and stratified by pooled site

More Istaroxime Patients Were Successfully Transitioned to Goal Directed Medical Therapy / Concomitant Meds at 96 hours – SEISMic B



Adverse Events in SEISMIC B

Event	Istaroxime (N=19)	Placebo (N=11)
All adverse events	15 (79%)	5 (46%)
Thrombocytopenia	0	2 (18%)
Cardiac failure	2 (11%)	3 (27%)
Atrial fibrillation	1 (5%)	0
Myocardial ischemia	1 (5%)	0
Ventricular extrasystoles	0	1 (9%)
Ventricular tachycardia	2 (11%)	1 (9%)
Infection	3 (16%)	1 (9%)
Metabolism and Nutrition	3 (16%)	3(27%)
Headache	2 (11%)	0
Adverse drug reactions		
Gastrointestinal (Nausea/Vomit)	2 (11%)	0
Infusion site pain/inflammation	9 (47%)	0

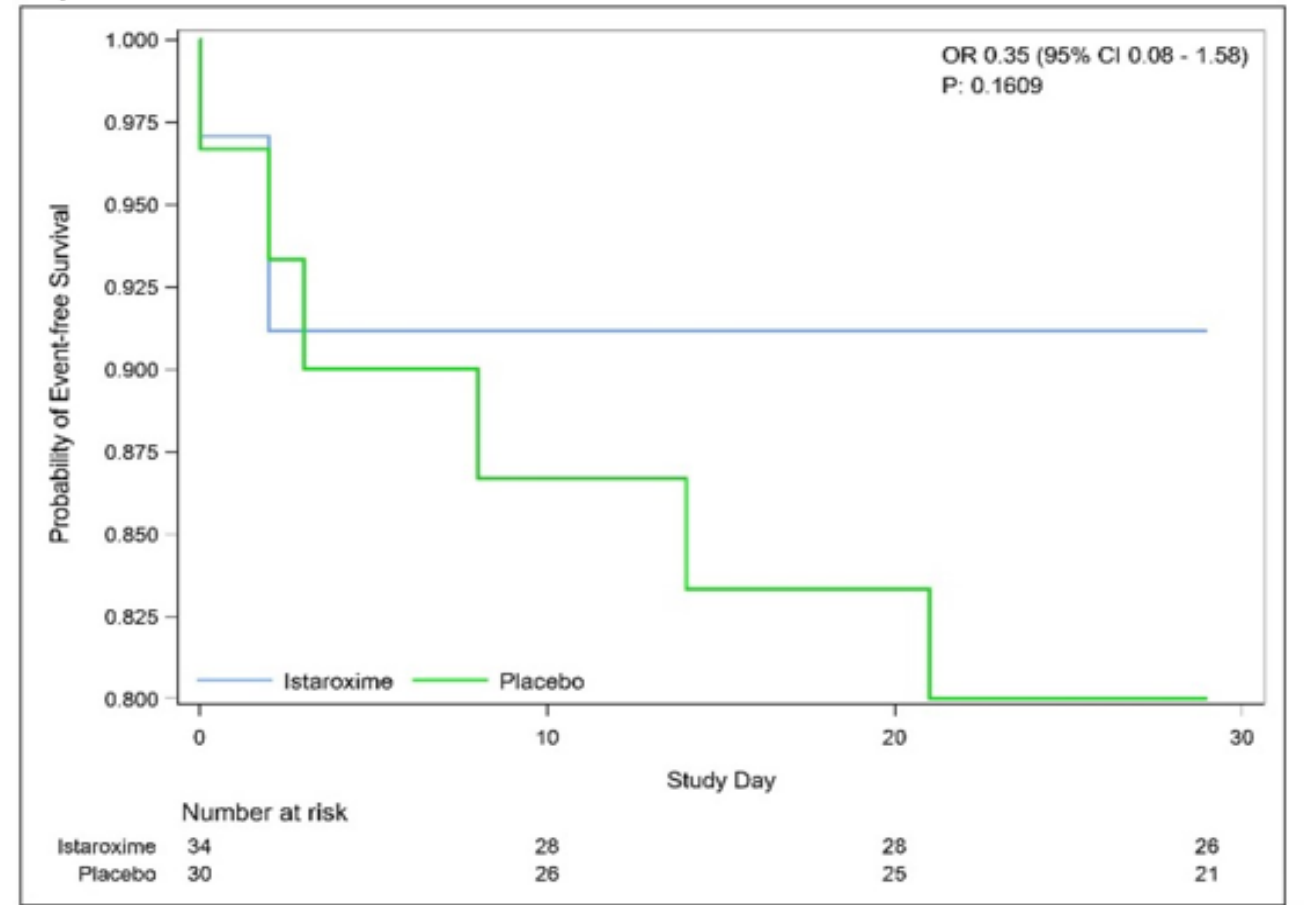
Serious Adverse Events in SEISMIC B

Event	Istaroxime (N=19)	Placebo (N=11)
All serious adverse events	2 (11%)	3 (27%)
Cardiac Failure (Worsening HF)	1 (5%)	2 (18%)
Cholecystitis	0	1 (9%)
Infection	2 (11%)	0
Arterial hemorrhage	0	1 (9%)

Positive Trend in Composite Endpoint:

Time to Worsening Heart Failure AE, Heart Failure Readmission or Death through 30 days

– SEISMic A (1.0) + B



3 patients have not yet completed 30 days in SEISMic B

Study Results Summary

- ✓ Systolic blood pressure significantly increased with istaroxime. The increase was rapid and sustained through the infusion period
- ✓ Key secondary endpoints of systolic and diastolic cardiac function such as cardiac output and filling pressures (PCWP) were significantly improved
- ✓ Mixed venous oxygen saturation (SVO₂), an assessment of organ perfusion, was significantly improved by 12 hours and remained significant through 48 hours
- ✓ Renal function was significantly improved and maintained over time compared to placebo
- ✓ The New York Heart Association (NYHA) classification of heart failure severity significantly decreased in the istaroxime group, and more patients subsequently transitioned to Goal Directed Medical Therapy.
- ✓ The istaroxime safety profile was favorable and generally consistent with what has been previously reported in other istaroxime clinical trials. Serious adverse events were infrequent in both the istaroxime and placebo groups (10.5% vs. 27.3%, respectively) and worsening heart failure reported as a serious adverse event occurred less frequently in the istaroxime group compared to placebo 5.3% versus 18.2%, respectively. Importantly, Istaroxime did not increase clinically significant arrhythmias compared to the placebo group.

Cardiogenic Shock Development Strategy

Focus on thoroughness, speed and relatively low cost of trials

SEISMic Study (Part A)

- Completed, positive Phase 2 Study
- SCAI Stage B due to AHF

SEISMic Part B Study

- Extended and titrated dosing for optimization
- Additional characterization of SERCA2a effect

SCAI Stage C

- Gain experience in more severe SCAI stage C patients with active comparator

Phase 3*

- Execute EOP2 meeting with these 3 studies augmented by AHF safety data base, etc.

Expected Steps to Phase 3 Readiness

Professor Alexandre Mebazaa, MD, PhD, FESC

Cardiogenic Shock

Specialty: Anesthesiology and Critical Care
Institute: Hôpital Lariboisière, Paris, France
Function: Chairman of the Department of Anesthesia and Critical Care

University positions

2000-now **Professor in Anesthesiology and Critical Care Medicine**, Paris Diderot School of Medicine,
2019– 2024 **Director of the “Biotherapy in the critically ill” team (U 942) funded by Inserm (french NIH)**, 42 Boulevard de la Chapelle, 75010, Paris, France

Clinical activities

2012- now Chairman of the Department of Anesthesia and Critical Care (57 ICU beds and 40 anesthesia rooms), Hôpitaux Universitaires Saint-Louis & Lariboisière Hospitals, 2 Rue A Paré, 75475 Paris Cedex 10, Paris, France

Research activities (2018-2020)

Our group perform pre-clinical models (mouse and rats) of heart failure, cardiogenic or septic shock. We perform biotherapies experiment, cardiovascular monitoring and biochemistry on plasma and tissues. This program is led by N Vodovar and JL Samuel, basic researchers. Concerning clinical research on critically ill patients, the group carries large national (eg FROG-ICU) and international surveys (eg ADRENOSS program, the GREAT network), collecting demographic and biobank in 50 countries. We also perform multiple national and international large randomised trials on cardiovascular and sepsis areas (STOP-or-NOT; Adrenoss-2; STRONG-HG). Clinical research is performed by Prof A Mebazaa (cardiovascular), Prof M Legrand (renal), Prof E Gayat (biostatistics, novel technologies).

Publications and fellowship: *promoting young fellow toward excellence*

A Mebazaa published 300+ articles on PubMed that are referenced more than 12,000 times and the H-index is 50+. M Legrand and E Gayat have also outstanding publication records.

For 2018, the group already published 50+ papers including original papers or reviews in the highest impact factor journal in intensive care or cardiology (Intensive care Medicine, Eur Heart Journal, Journal of the American College of Cardiology).

The group has an international recognition in “novel biotherapies in critical conditions” and already include 2-4 fellows/year, intensivists or cardiologists from Europe and Asia. Fellows that stayed in the lab several months and up to 2 years, left with numerous publications and academic promotions when back home.



Cardiogenic Shock Represents a Significant Opportunity for Istaroxime and Windtree

- ✓ Significant opportunity for Istaroxime to make a difference:
 - ~20-30% mortality in classic shock and high morbidity
 - Very long median length of hospital stay (~ 10 days¹) means high cost of hospital care (estimated >\$175k²) and creates opportunity for pharmacoeconomic benefits
- ✓ Currently available pharmacologic treatments have undesirable side effects and can result in poor outcomes
- ✓ Lack of competition in development or active competition in the market
- ✓ Attractive \$1.25B valuation of market potential versus time and cost of development supports potential deals



¹ US Hospital Claims Data, 2022

² Healthcare.gov, Department of Health & Human Services, estimated from average cost of hospital stay

³ Long et al, USC Cardiology Review, Describing and Classifying Shock: Recent Insights, Sept 2021

What Would the Ideal Treatment for Cardiogenic Shock due to Heart Failure Look Like? (Our Objective)

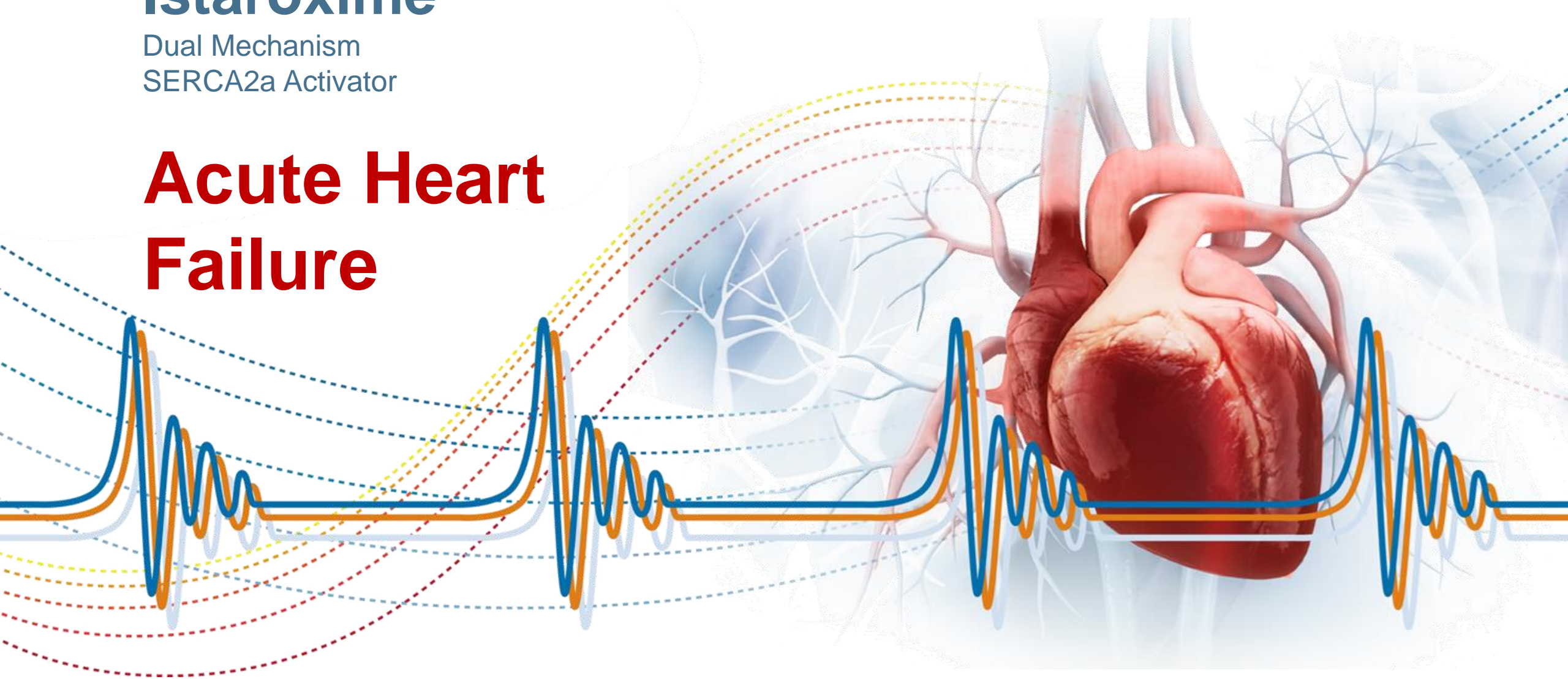
- ✓ Improves systolic and diastolic cardiac function--the root cause of cardiogenic shock
- ✓ Improves blood pressure and organ perfusion--the main problem in cardiogenic shock
- ✓ Avoids harming the kidneys
- ✓ Does not increase heart rate or increase myocardial oxygen demand or energy requirements of the heart
- ✓ Does not increase or cause cardiac arrhythmias
- ✓ Contributes to effective diuresis and resolving fluid overload in lungs and body
- ✓ Rapid onset of action with a predictable effect that can be titrated to individual patients

Istaroxime data to date demonstrate a unique and compelling profile and opportunity to be a better treatment for cardiogenic shock and low blood pressure acute heart failure patients

Istaroxime

Dual Mechanism
SERCA2a Activator

Acute Heart Failure



Heart Failure –

A Large and Growing Market with Significant Mortality and Unmet Need

#1 cause of U.S. hospitalization in patients > 65 years old

Annual Admissions

~1.3M U.S.



~1.5M E.U.

Patients

7M U.S.,

25M+ worldwide



~7%

In-patient mortality

30-day mortality can exceed 10%



>\$18B

annual U.S. hospital costs

Most expensive of the Medicare diagnoses



0

New pharmacologic advancements in acute heart failure for decades



Lack of therapeutic advances led the FDA to issue new Heart Failure Guidance in July 2019 for greater development flexibility in acceptable endpoints, specifically acknowledging mortality is not required

Istaroxime – Acute Heart Failure

Development Strategy

Regional Strategy: Licensing Partner in Asia / Pac Intends to Start Phase 3 AHF Study

Global Phase 3 AHF Program Strategy



Augment our data from the positive phase 2a and phase 2b AHF studies with the efficacy, safety and dosing and characterization learnings from the extension and other studies in the severe AHF patients experiencing cardiogenic shock. If positive and adequate, move istaroxime into phase 3 for AHF.



Our strategy is to focus on treating heart failure patients with low blood pressure, who also tend to be diuretic resistant, as a patient population that we believe could particularly benefit from the unique profile and potential ability of istaroxime to increase cardiac function and increase blood pressure while maintaining or improving renal function.

Currently seeking partnership to finance global program

Next Generation, Oral SERCA2a Activators Platform has Potential for *both Major Types* of HF in Acute *and* Chronic Therapy

Today:

Istaroxime

- Dual Mechanism (SERCA2a & Na⁺/K⁺)
- IV only, Acute Heart Failure with Reduced Ejection Fraction (HFrEF) with normal / low blood pressure

Development Strategy:

AHF Hospital, i.v.
HFrEF

Future:

Preclinical Dual Mechanism, (SERCA2a & Na⁺/K⁺) Activators

- Same mechanism as Istaroxime with potential for oral / chronic use
- Granted composition of matter IP (U.S. and EU)
- Strategy: Fast follow-on to Istaroxime in AHF; then add on hospital discharge / chronic use development

AHF Hospital, i.v.	CHF Home, oral
HFrEF	

&

Preclinical Pure SERCA2a Activators

- Innovative pure SERCA2a activator (without the Na⁺/K⁺ mechanism) with newly granted composition of matter IP (EU)
- Develop for Heart Failure including Preserved Ejection Fraction (HFpEF) for chronic and acute use

AHF Hospital, i.v.	CHF Home, oral
HFrEF	HFpEF

Windtree Strategy for Value Creation – Deliver Data and Deals

2024 Accomplishments

- ✓ FPI global Phase 2b Extension Study of istaroxime in Cardiogenic Shock
- ✓ \$138MM plus royalties' regional license secured for CV products
- ✓ Eliminated \$15MM in liabilities with Deerfield, added to shareholder equity
- ✓ Delivered positive data with istaroxime and the pure SERCA2a in arrhythmias
- ✓ Started concomitant therapy Stage C study in more severe shock patients
- ✓ Acquired a novel pre-clinical atypical Protein Kinase C iota platform

2H 2024 / 1H 2025

Focus and Planned Deliverables¹

- Positive istaroxime Phase 2b SEIMiC part B Study Results in Cardiogenic Shock (CS)
- Execute istaroxime study in Stage C CS with interim data planned for late Q1 2025
- Support our license partner start up of Phase 3 Acute Heart Failure study in Asia/PAC
- Secure additional licenses for istaroxime and SERCA2a activators
- aPKCi inhibitor IND-enabling studies
- Drive capital efficacy and partnerships



Financial and Deal Summary

Cash*

June 30, 2024	\$1.8M
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Common Stock Outstanding

September 13, 2024	1,610,734
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* Pre-July PIPE financing

Completed Deals- \$217MM in Potential Milestones Plus Royalties

- **Istaroxime, Dual-Mechanism SERCA2a Activators, Rostafuroxin**
 - Exclusive Greater China regional license to Lee's Pharm
 - Potential proceeds: Up to **\$138.1 million** in potential milestone payments, low double-digit % royalties; Partner pays for development, regulatory and commercial costs
- **AEROSURF / KL4 Platform –**
 - Exclusive global license to Lee's Pharm and Zhaoke
 - Potential proceeds: Up to **\$78.9 million** in potential milestone payments, low double-digit % royalties; Partner pays for all costs

Potential Next Deal

- **Global (ex-Greater China) license for Istaroxime, SERCA2a Activators**



WINDTREE
THERAPEUTICS™