



# Windtree Therapeutics Company Overview

August 26, 2022



**WINDTREE**  
THERAPEUTICS™

(NASDAQ: WINT)

# Forward-Looking Statements

This presentation includes forward-looking statements within the meaning of Section 27A of the Securities Act of 1933, as amended, and Section 21E of the Securities Exchange Act of 1934, as amended. These statements, among other things, include statements about the Company's clinical development programs, business strategy, outlook, objectives, plans, intentions, goals, future financial conditions, future collaboration agreements, the success of the Company's product development activities, or otherwise as to future events. The forward-looking statements provide our current expectations or forecasts of future events and financial performance and may be identified by the use of forward-looking terminology, including such terms as “believes,” “estimates,” “anticipates,” “expects,” “plans,” “intends,” “may,” “will,” “should,” “could,” “targets,” “projects,” “contemplates,” “predicts,” “potential” or “continues” or, in each case, their negative, or other variations or comparable terminology, though the absence of these words does not necessarily mean that a statement is not forward-looking. We intend that all forward-looking statements be subject to the safe-harbor provisions of the Private Securities Litigation Reform Act of 1995. Because forward-looking statements are inherently subject to risks and uncertainties, some of which cannot be predicted or quantified and some of which are beyond our control, you should not rely on these forward-looking statements as predictions of future events. The events and circumstances reflected in our forward-looking statements may not be achieved or occur and actual results could differ materially from those projected in the forward-looking statements. These risks and uncertainties are further described in the Company's periodic filings with the Securities and Exchange Commission (“SEC”), including the most recent reports on Form 10-K, Form 10-Q and Form 8-K, and any amendments thereto (“Company Filings”). Moreover, we operate in an evolving environment. New risks and uncertainties may emerge from time to time, and it is not possible for management to predict all risks and uncertainties. Except as required by applicable law, we do not plan to publicly update or revise any forward-looking statements contained herein, whether as a result of any new information, future events, changed circumstances or otherwise.

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# Windtree Therapeutics and Istaroxime Highlights



**Biopharmaceutical company with advanced clinical focused on significant acute CV markets with high unmet needs and with supportive regulatory paths and designations (NASDAQ: WINT)**



**Through three Phase 2 global studies, lead asset istaroxime has consistently demonstrated a highly unique and attractive profile**

- It is the only acute heart failure or shock drug that has demonstrated both significant improvement in cardiac function of a failing heart, as well as rapid and significant improvement in blood pressure, with what so far has been a differentiating safety profile (avoiding many of the use-limiting side effects of existing therapies)



**Recent positive Phase 2 study with istaroxime in early cardiogenic shock (ECS) paves the way for what we believe is a relatively fast and less expensive developmental and regulatory pathway**

- Precedent shows blood pressure response can be acceptable as the primary endpoint in a pivotal shock study. Additionally, istaroxime demonstrated significant other benefits that we expect will continue to help us build a strong evidence-based position in the larger Phase 3 planned for 2023.
- Given what we believe to be an attractive opportunity that may be pursued with less spend and have faster time to market, Cardiogenic shock has become the organization's priority and focus

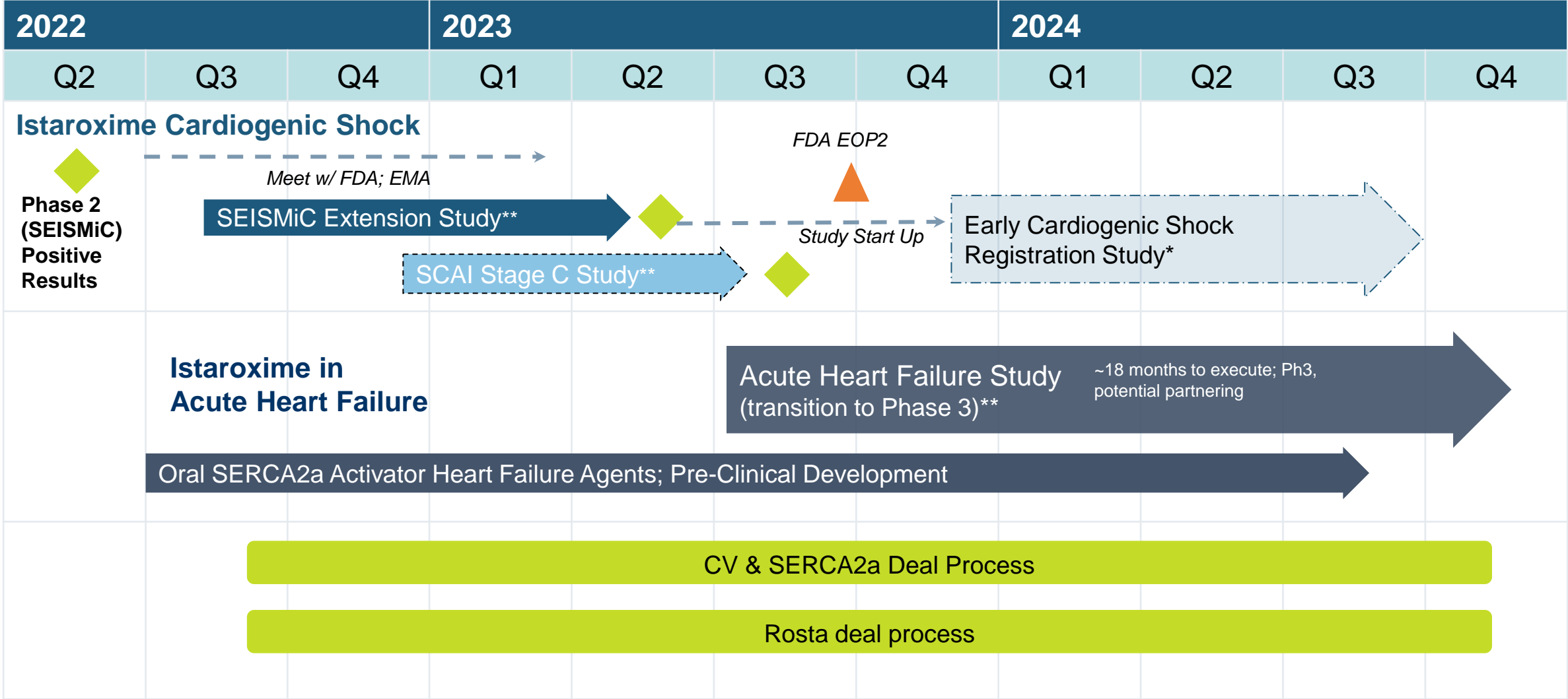


**Highly experienced management team and company leadership**

# Pipeline

Lead Products	Indication	Phase	Development Status	Regulatory Status
<b>Istaroxime</b>	Acute Heart Failure	Phase 2b	<ul style="list-style-type: none"> <li>Plan a second Phase 2b clinical trial in ~300 patients targeted to start once clinical trial operations are fully funded</li> </ul>	<i>FDA Fast Track Designation</i>
<b>Istaroxime</b>	Early Cardiogenic Shock	Phase 2	<ul style="list-style-type: none"> <li>Positive Phase 2 study</li> <li>Planning the execution of the next studies and plans to meet with regulatory agencies regarding development path</li> </ul>	<i>Potential for Breakthrough Designation</i>
<b>Oral SERCA2a Activators</b>	Chronic HF; potentially HFpEF	Preclinical	<ul style="list-style-type: none"> <li>Chronic and Acute Heart Failure</li> <li>Target for collaboration/partnership</li> </ul>	<i>Preclinical</i>
<b>Rostafuroxin</b>	Genetically Associated HTN	Phase 2b	<ul style="list-style-type: none"> <li>Out-licensing opportunity</li> </ul>	
<b>KL4 Surfactant – COVID 19</b>	COVID 19 Pilot; Possible invasive Tx for RDS in neonates	Phase 2	<ul style="list-style-type: none"> <li>Study completed; Results presented March 2022</li> <li>Global out-license to Lee's Pharmaceuticals</li> </ul>	<i>FDA, EMA Orphan Drug for RDS</i>
<b>AEROSURF / Aerosolized KL4</b>	KL4 surfactant Drug/Device Tx for RDS	Phase 2b	<ul style="list-style-type: none"> <li>Global out-license to Lee's Pharmaceuticals</li> </ul>	<i>FDA Fast Track Designation, Orphan Drug</i>

# Strategy for Value Creation







# Istaroxime

## Early Cardiogenic Shock

*Additional potential indication in active clinical development*

# Cardiogenic Shock

**A severe presentation of heart failure** characterized by **very low blood pressure and hypoperfusion** accompanied by high filling pressures of the heart and decreased urine output. It is a **treatment emergency**



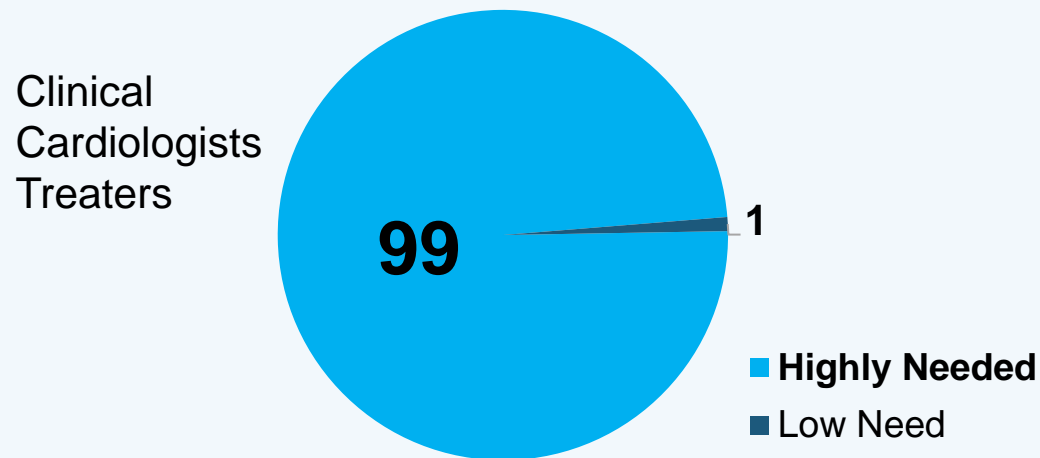
- Caused by severe impairment of cardiac function that results in diminished cardiac output, end-organ hypoperfusion and hypoxemia
- Commonly requires pharmacological or mechanical intervention to increase SBP to >90mmHg and improve tissue perfusion
- High in-hospital mortality (~30-40%) and substantial morbidity in survivors<sup>1</sup>
- Represents an approximate \$1.25B total market potential<sup>2</sup>

# Early Cardiogenic Shock Treatment

## Istaroxime Potential Opportunity to Address Significant Unmet Need

- No satisfactory pharmacological intervention to reverse the conditions
  - 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” for severe cases
- A therapy that can be used **earlier** to rapidly **improve blood pressure and cardiac function without unwanted side effects** is needed

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



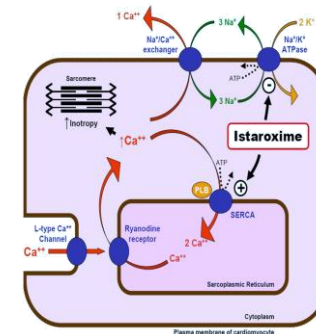
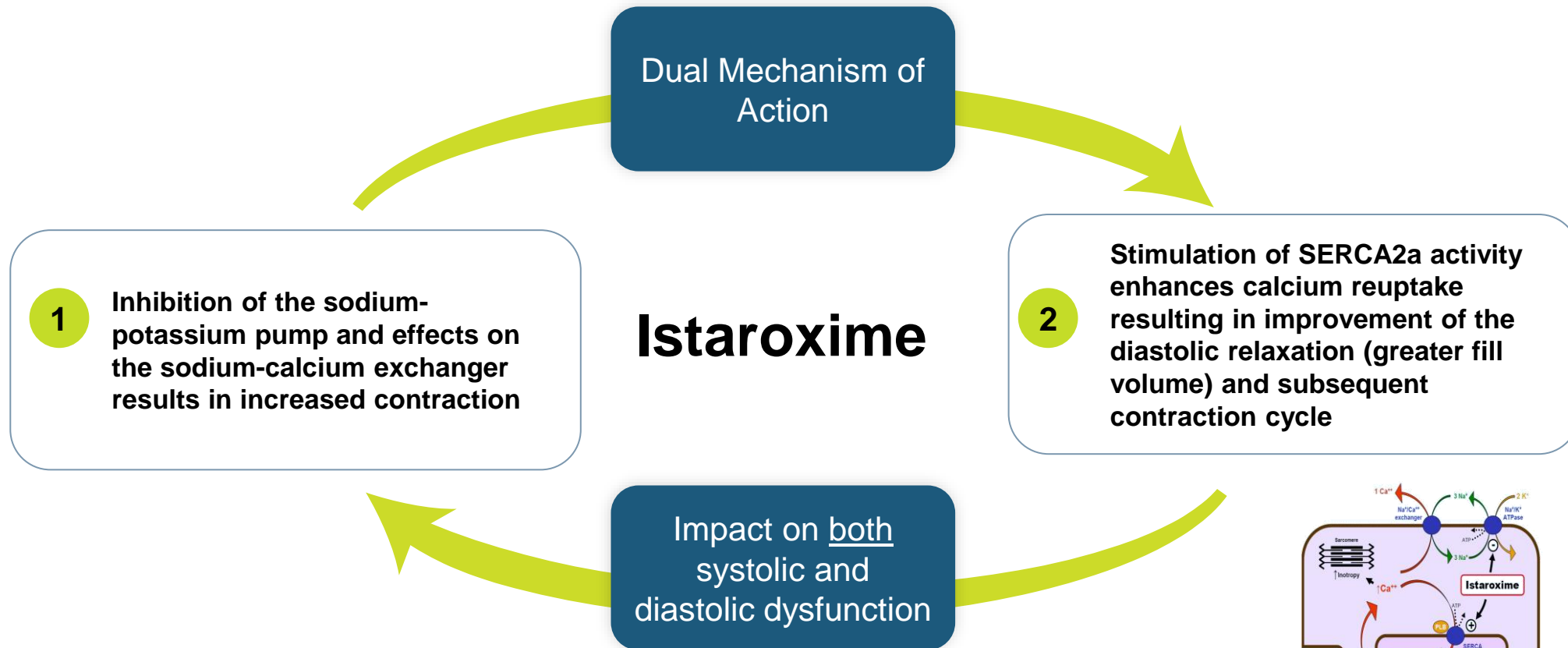
✓ **84%** of the cardiologists responded they would be **likely to extremely likely to use** istaroxime for early cardiogenic shock patients

✓ 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

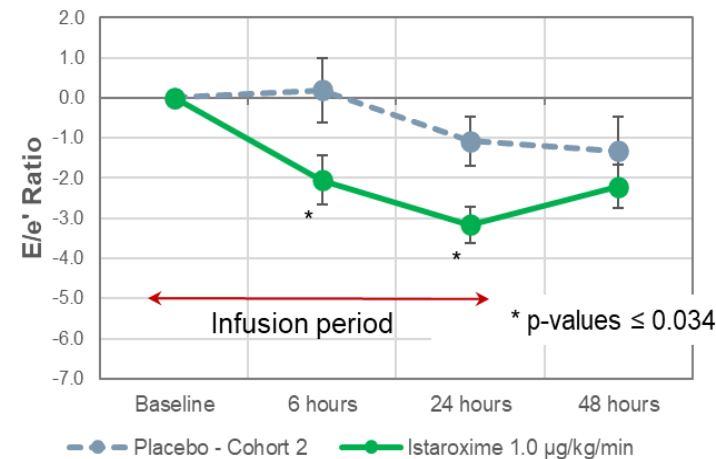
Novel intravenous agent designed to improve  
systolic contraction and diastolic relaxation of the heart



# Rationale for Istaroxime in Cardiogenic Shock Came from AHF Phase 2 Trials

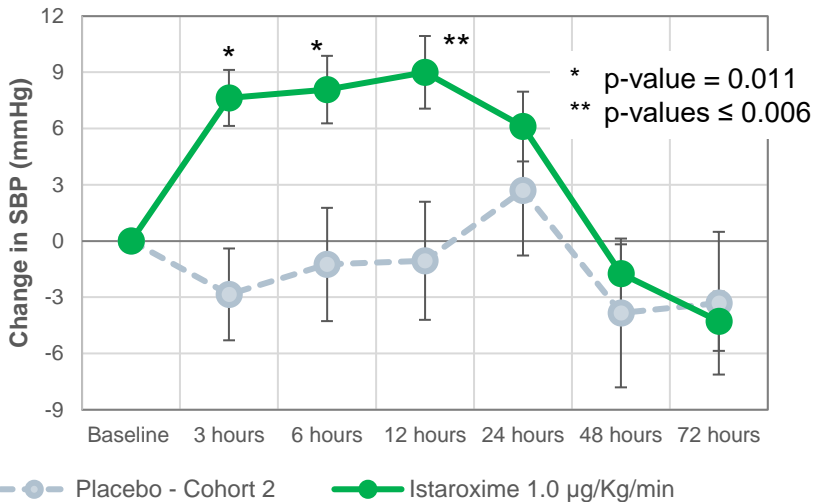
## E/e' (cardiac filling pressure)

Istaroxime 1.0 µg/kg/min vs. placebo



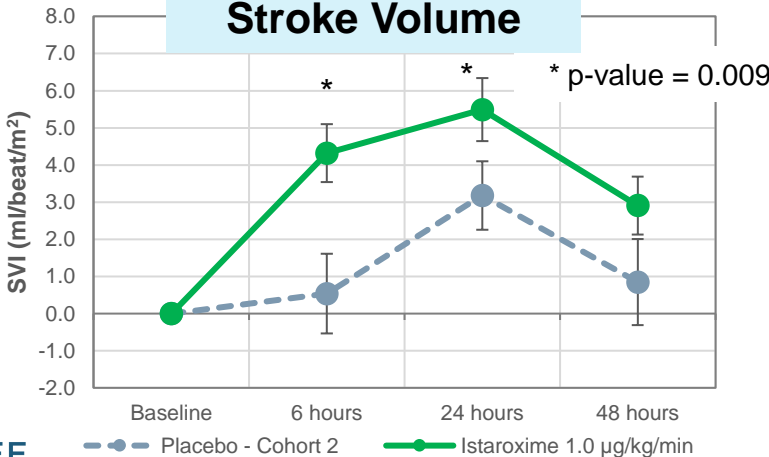
## Systolic Blood Pressure (SBP)

Istaroxime 1.0 µg/kg/min vs. placebo

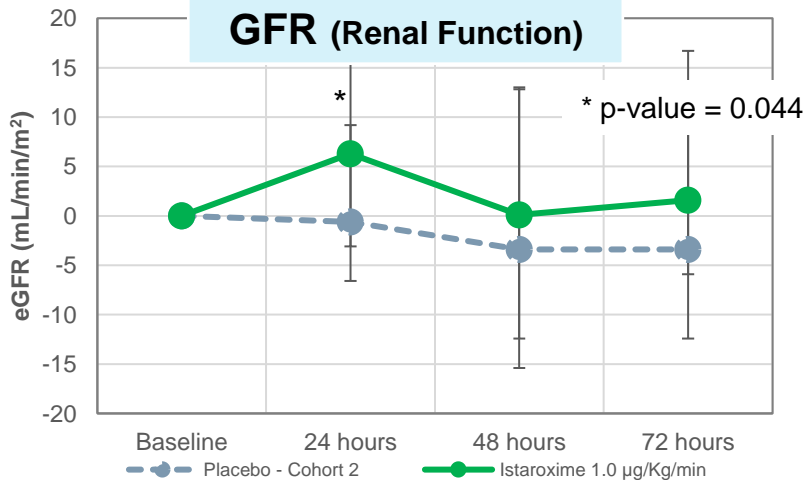


Improved cardiac function and SBP along with a favorable renal and tolerance profile

## Stroke Volume



## GFR (Renal Function)



# Early Cardiogenic Shock Treatment

## Istaroxime Potential Opportunity for Accelerated Pathway

**Potential for a relatively fast and less expensive developmental and regulatory pathway**

***FDA Regulatory  
Commentary with  
Break-Through  
Therapy Designation  
Potential***

Sponsors are potentially **not required to show benefit other than an increase in blood pressure to support approval of drugs to treat hypotension in the setting of shock<sup>(1)</sup>**

Precedent NDA: Giapreza® (IV Angiotensin II), approved in 2017 for increasing MAP in distributive shock – a different type of shock, not a competitor to istaroxime in early cardiogenic shock)<sup>(2)</sup> Precedent also indicates potential accelerated regulatory pathway and review opportunities

# SEISMiC Early Cardiogenic Shock Study

*Clinical strategy: Start development with patients in early cardiogenic shock caused by severe heart failure*



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



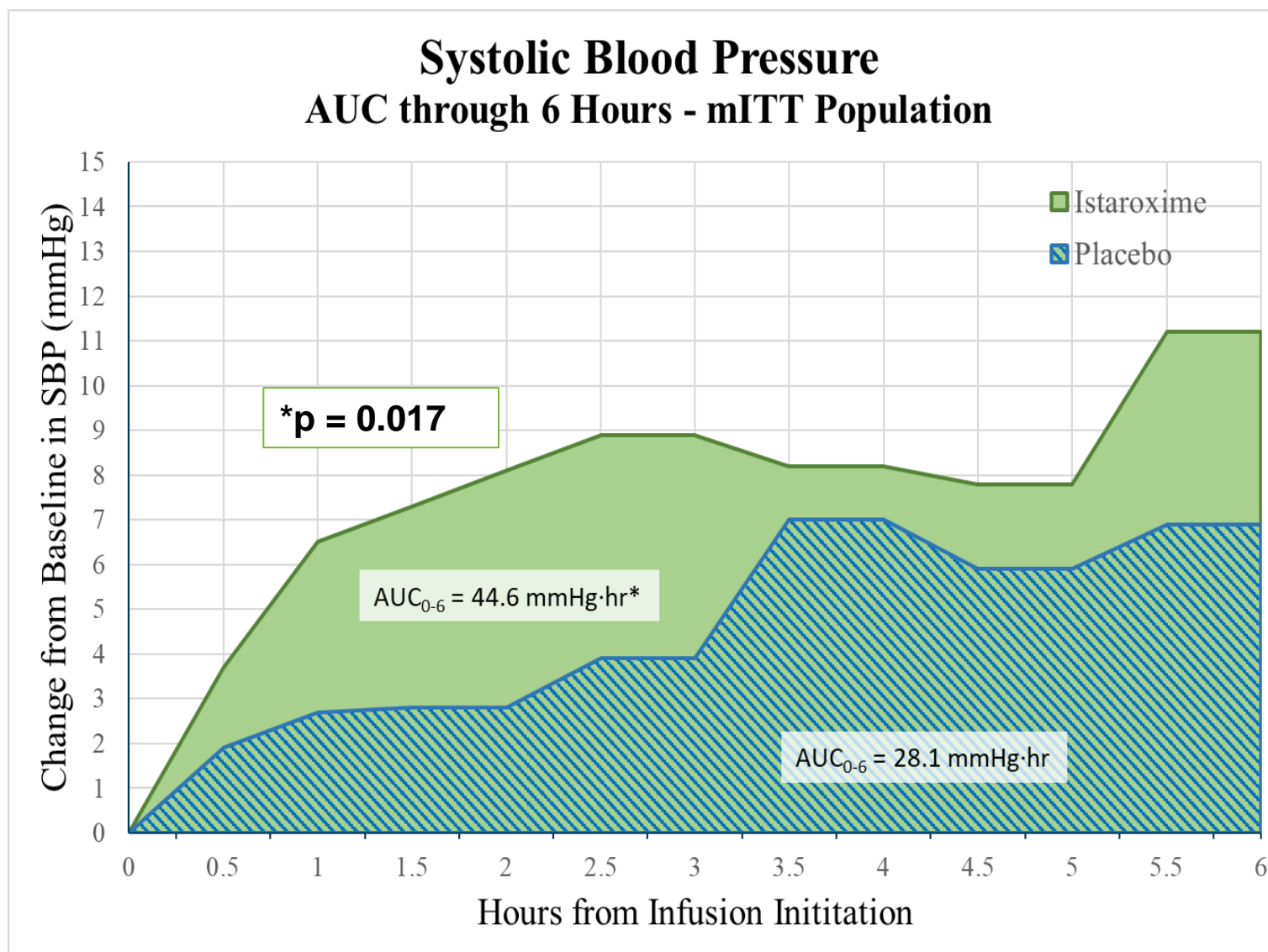
Study drug was infused for 24 hours in a 1:1 randomization to placebo or istaroxime. Two istaroxime target doses were evaluated, 1.5 $\mu$ g/kg/min in the first group and 1.0  $\mu$ g/kg/min in the next group.



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

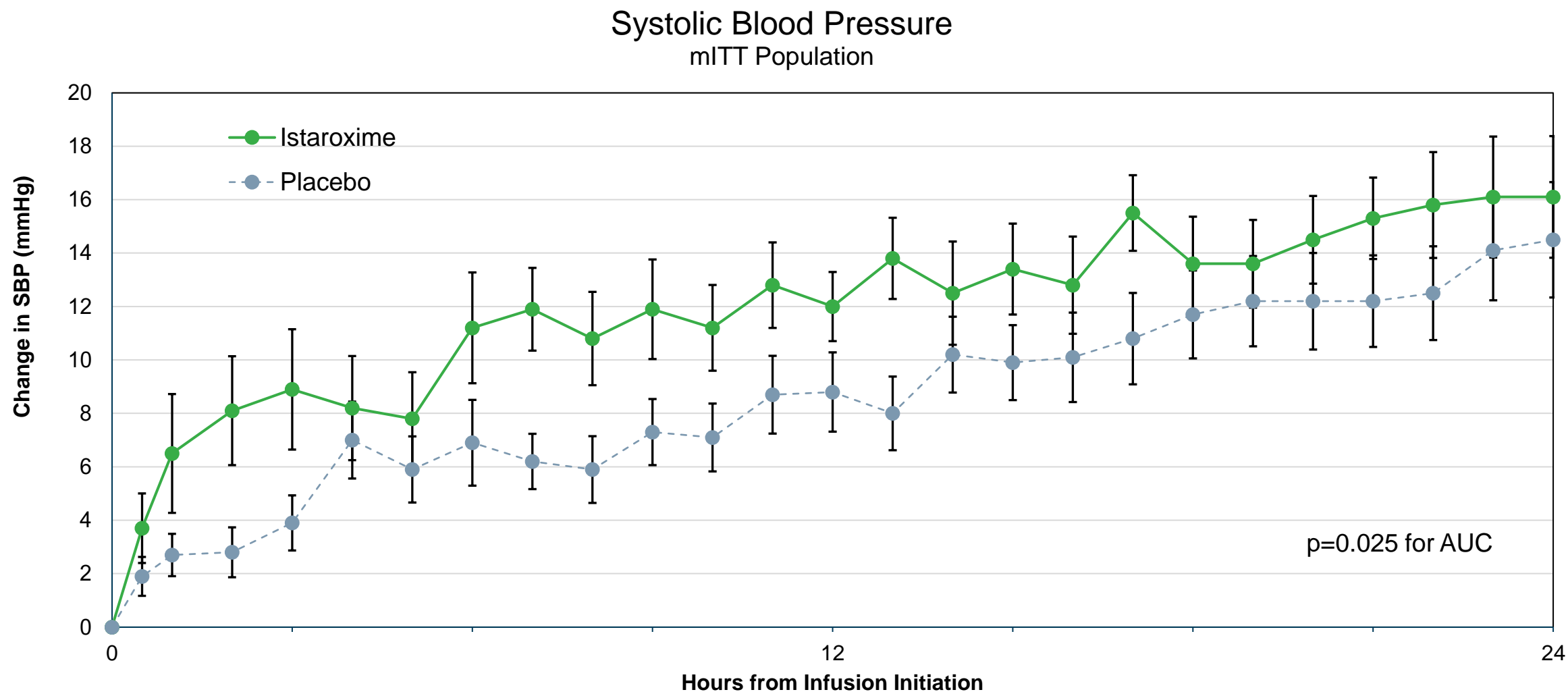
Secondary measures included: SBP profile at 24 hours, echocardiology measures associated systolic and diastolic cardiac function, renal function, various safety and tolerability measures

# Difference in SBP Profile





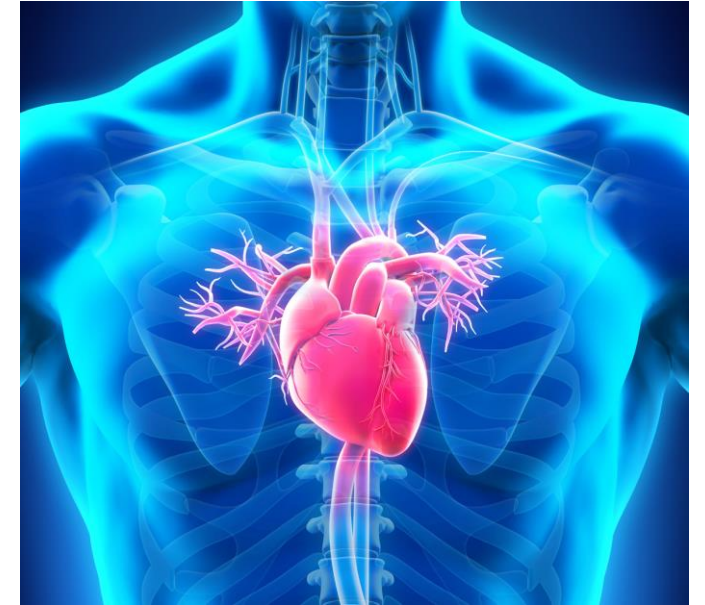
# Systolic BP Improvements Persisted over 24 Hours



# Cardiac Function Improvement

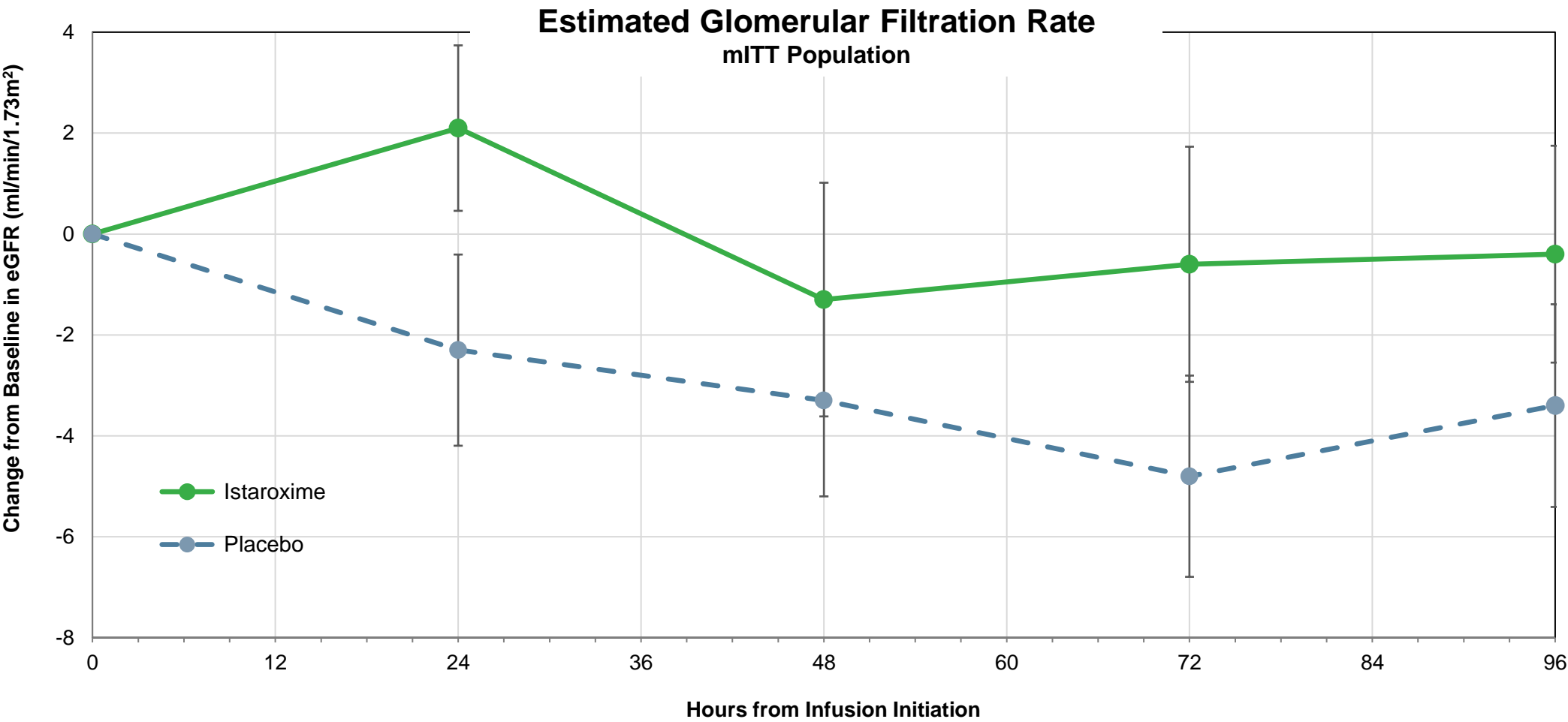
Echocardiography demonstrated improvements in key systolic and diastolic cardiac function measures including:

- **Cardiac index significantly increased**
- **Stroke volume index substantially increased**  
(4 mL/m<sup>2</sup>) approaching statistical significance
- Other echocardiographic measurements improved:
  - **Left atrial area was reduced**
  - **Left ventricular end systolic volume was reduced**
  - **Left ventricular end diastolic volume was reduced**



# Treatment was Associated with a Favorable Renal Profile

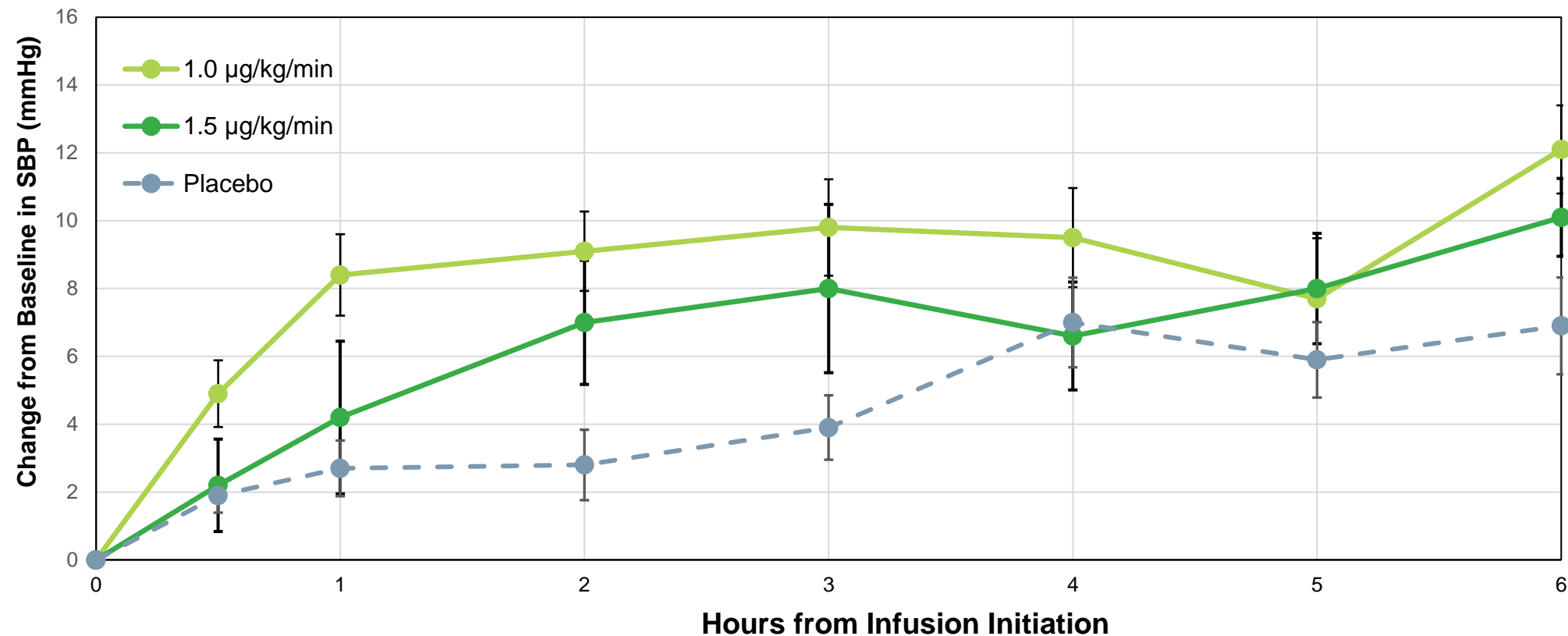
Renal function was not decreased in istaroxime treated patients



# 1.0 $\mu\text{g/kg/min}$ Produced a Favorable Effect on SBP

1.0  $\mu\text{g/kg/min}$  dosing was associated with:

- Early, rapid SBP increase and improvement in more echocardiographic assessments of cardiac function
- More favorable adverse event, serious adverse event and clinical event profile



# SEISMiC Results Summary

## SEISMiC was a positive study in early cardiogenic shock patients

- ✓ Systolic blood pressure significantly increased within the first 6 hours of initiating the infusion ( $p=0.017$ ) and the increase was maintained throughout the 24-hour infusion ( $p=0.025$ )
  - SBP increases were rapid within the first hour and sustained through the 96-hour post-infusion measure
- ✓ Key secondary endpoints of systolic and diastolic cardiac function and performance were improved
- ✓ Renal function was maintained
- ✓ SEISMiC provided valuable information for optimizing our dose moving forward
- ✓ These data substantiate and advance the rationale for istaroxime as a potential treatment for cardiogenic shock and support the existing data from the program in AHF

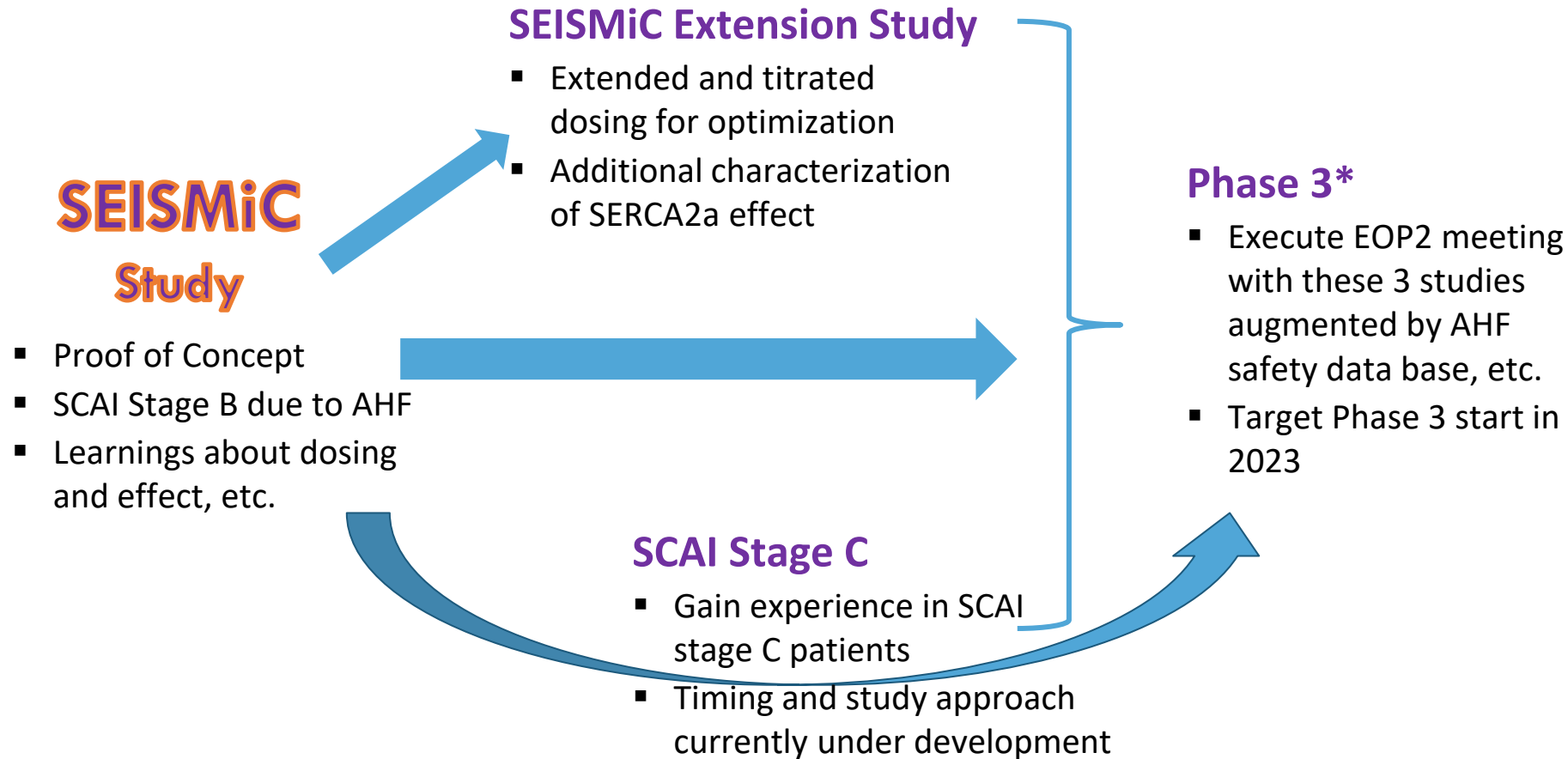


## Relevance to the Acute Heart Failure (AHF) Program

- The early cardiogenic shock trial results are consistent with Windtree's Phase 2 AHF studies and complementary to further advancement in AHF.
- While SEISMiC was an early cardiogenic shock study, the patients studied had very severe AHF providing valuable insight into treating more severe AHF patients.
- As an acute cardiac treatment:

**Istaroxime has the potential to effectively improve cardiac function  
without reducing SBP and/or renal function  
(common side effects of currently available rescue agents)**

# Cardiogenic Shock Development Strategy



*\* Study plans and progression to Phase 3 dependent upon regulatory alignment and resourcing*

# Plan for Dose Optimization – Extension Study

*Following the positive results in the early cardiogenic shock study, an extension study is planned to support ongoing development in early cardiogenic shock and acute heart failure*

## Study objectives:

- ✓ Advance the characterization of the physiology associated with longer istaroxime dosing as well as evaluate a dose titration
- ✓ More fully illuminate the effects and potential benefits associated with SERCA2a activation
- ✓ Support our regulatory strategy for istaroxime

## Current study plan design:



Double-blind, placebo controlled in up to 30 patients (2:1 randomization) with SBP between 70-100mmHg conducted in sites in the US, EU and LATAM



Two treatment arms of 60-hour infusions, titrating down from 1.0 starting dose  
Placebo controlled arm

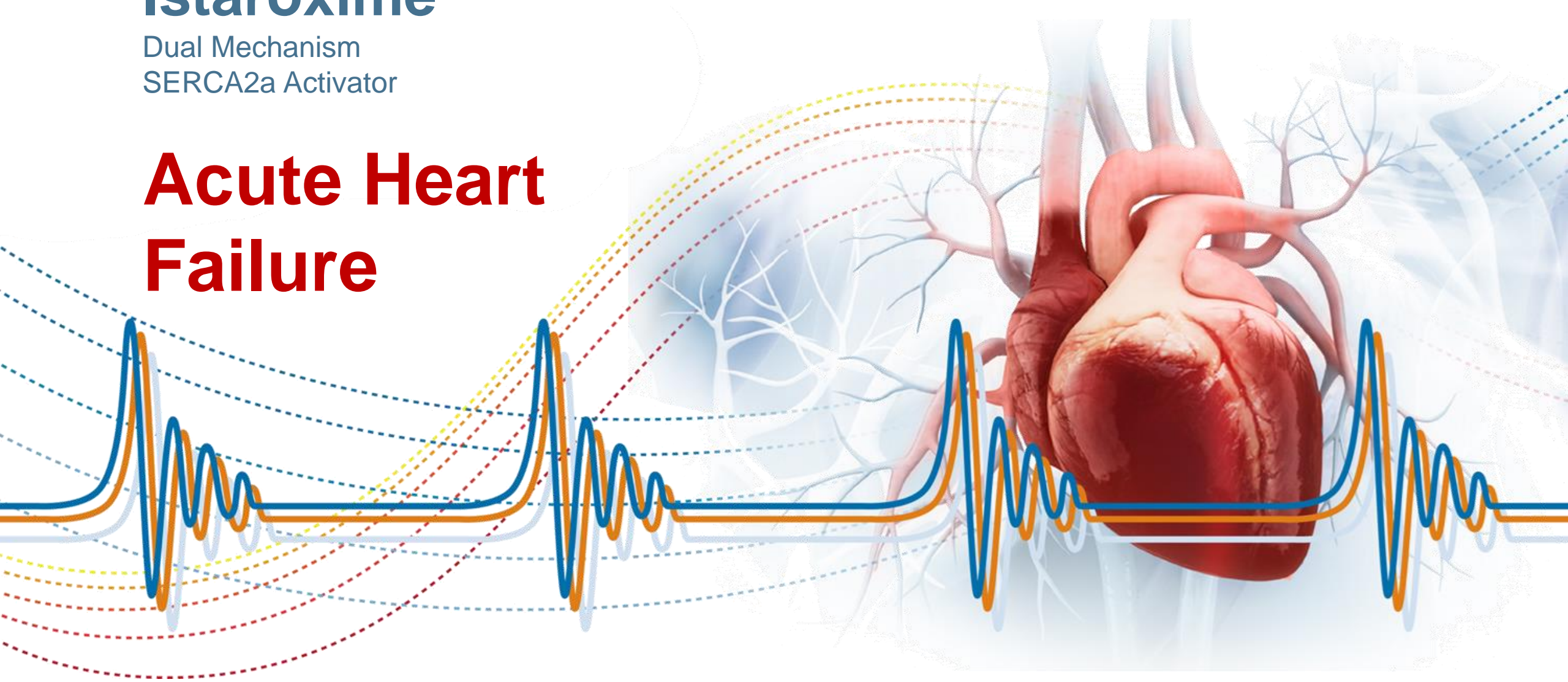


Multiple physiologic measures associated with cardiac function,  
blood pressure and safety  
Approximately 6 months of recruitment

# Istaroxime

Dual Mechanism  
SERCA2a Activator

## Acute Heart Failure



# Heart Failure – Large, Growing Market But Underserved

The prevalence and mortality of heart failure is high and increasing

**#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



# Acute Heart Failure – Significant Unmet Clinical Need

## Patient Management Goals

- **Clinical objectives** for AHF patient management include:
  - **Relieve pulmonary congestion** and general edema (e.g., “dry out”) with IV diuretics
  - **Improve cardiac function** and peripheral/organ perfusion
  - **Achieve stable, fully compensated** clinical state
  - Transition to oral, outpatient medicines (for chronic management of heart failure)

## Current Treatment Options

- **Current approaches to acutely improve cardiac function are associated with unwanted effects:**
  - Heart rhythm disturbances
  - Increased heart rate and myocardial oxygen demand
  - Decreased blood pressure
  - Potential damage to the heart muscle
  - Worsening renal function
  - Mortality
- **Patients with low blood pressure (SBP) and peripheral hypoperfusion are high risk, challenging patients who are also generally resistant to diuretic therapy and often discharged in a sub-optimal state**

# Istaroxime AHF Phase 2a & 2b Studies

## Phase 2a



n=120  
ADHF Patients



Dosing=  
**0.5, 1, 1.5** µg/kg/min



**6 hour**  
Infusion

- Primary: PCWP significantly improved
- Stroke Vol & SBP – significant increase
- Heart Rate (HR) - lowered

## Phase 2b

n=120  
ADHF Patients  
(dyspnea plus need  
for IV furosemide ≥ 40mg)

Dosing=  
**0.5, 1.0** µg/kg/min

**24 hour**  
Infusion

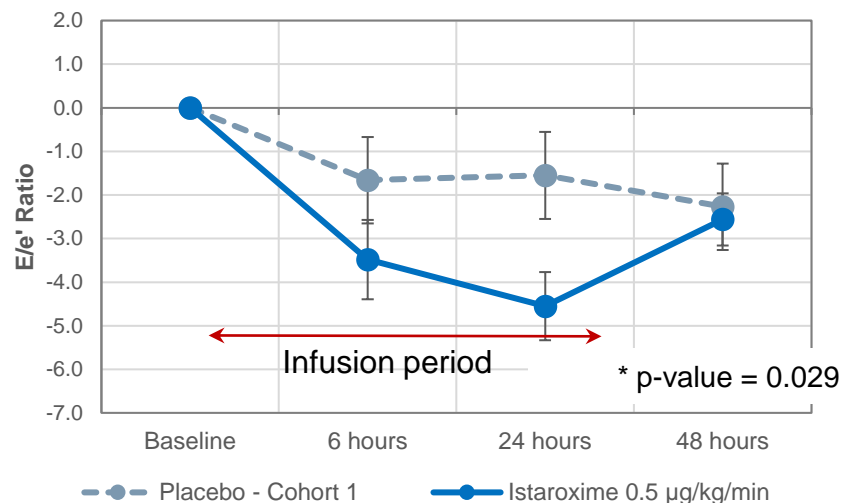
### Results

Positive Phase 2 trial results demonstrated improved cardiac function  
**without unwanted side effects of existing rescue therapies**

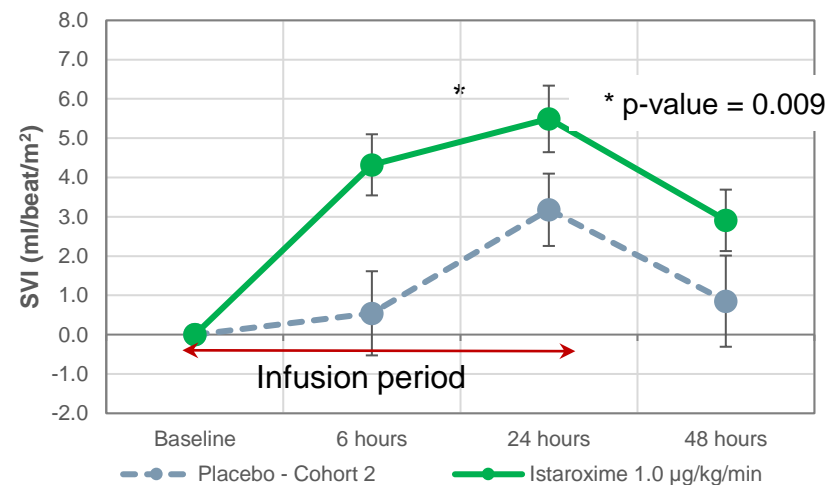
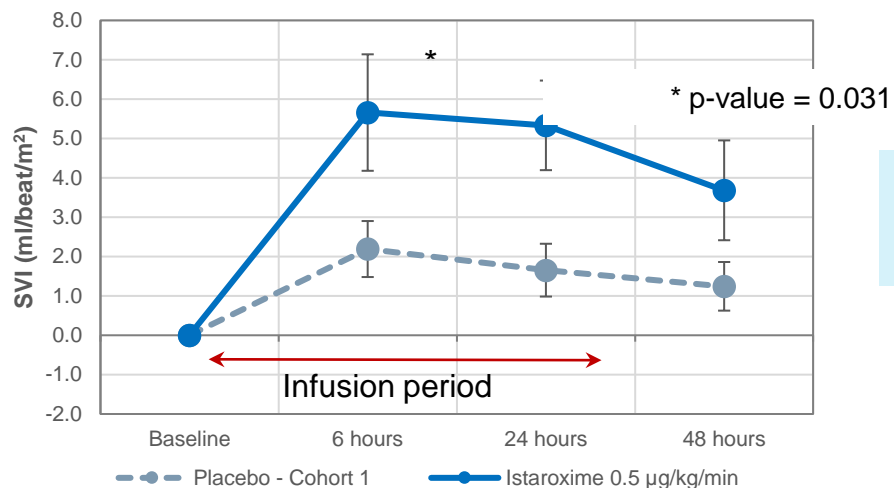
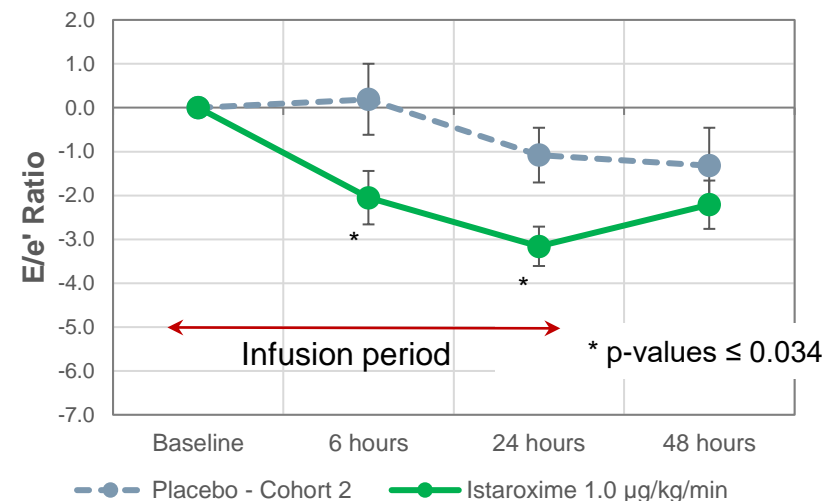
# Primary Endpoint Achieved

## Significant Changes in E/e' Ratio<sup>1</sup> and Stroke Volume

Istaroxime 0.5 µg/kg/min vs. placebo

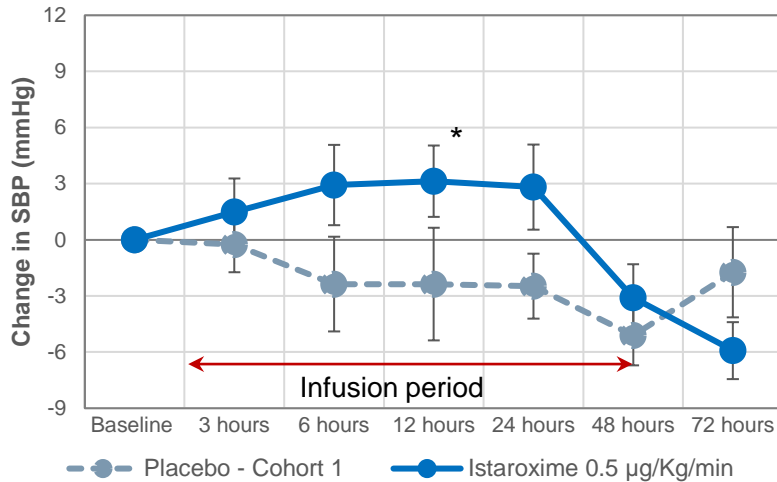


Istaroxime 1.0 µg/kg/min vs. placebo



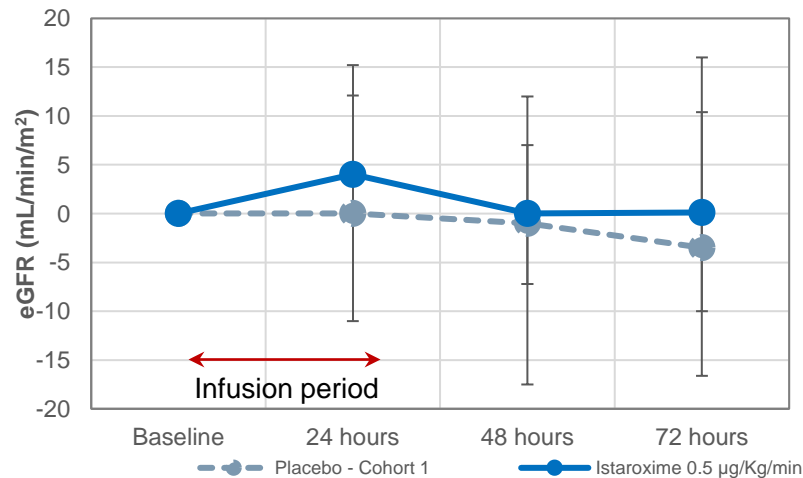
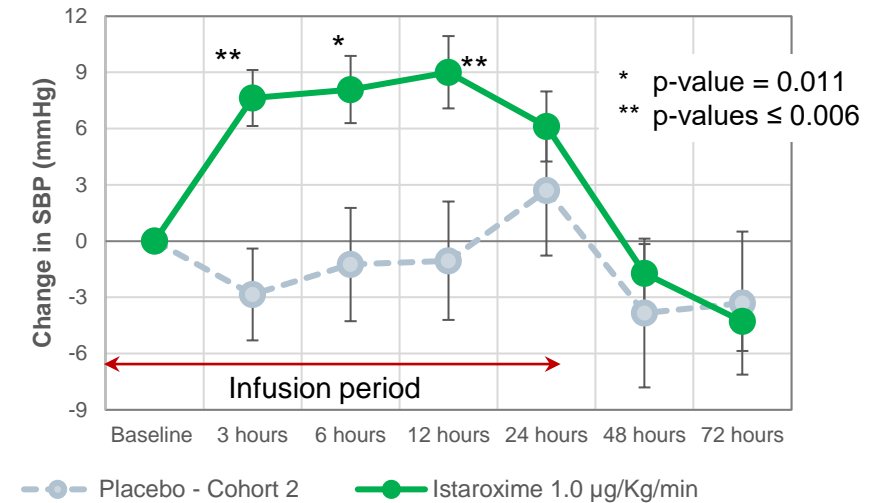
# Systolic Blood Pressure Increased During Treatment and Renal Function Tended to Improve

Istaroxime 0.5 µg/kg/min vs. placebo

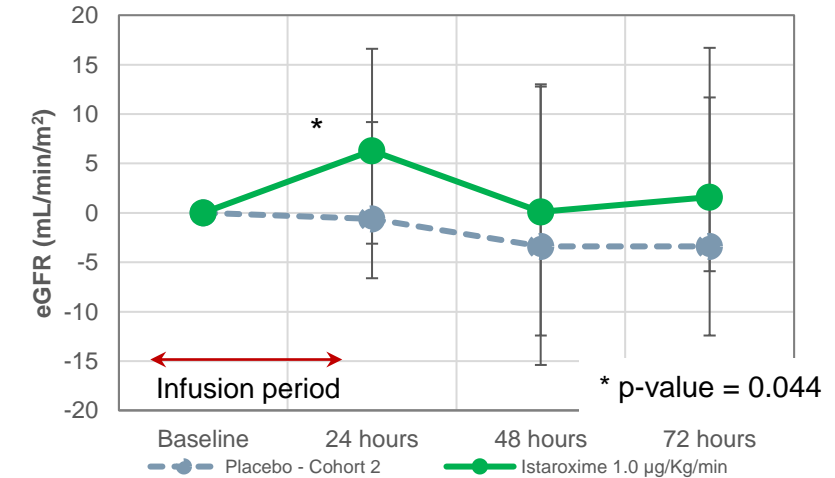


**Systolic  
Blood  
Pressure  
(SBP)**

Istaroxime 1.0 µg/kg/min vs. placebo

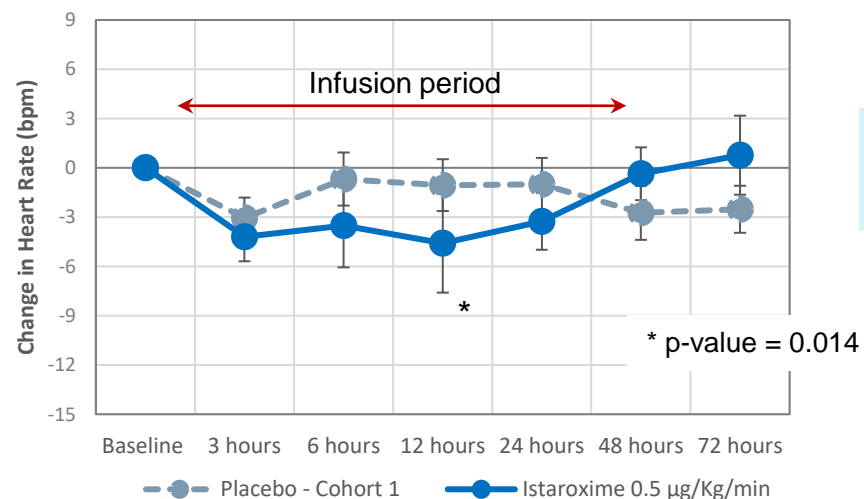


**GFR  
(Renal  
Function)**



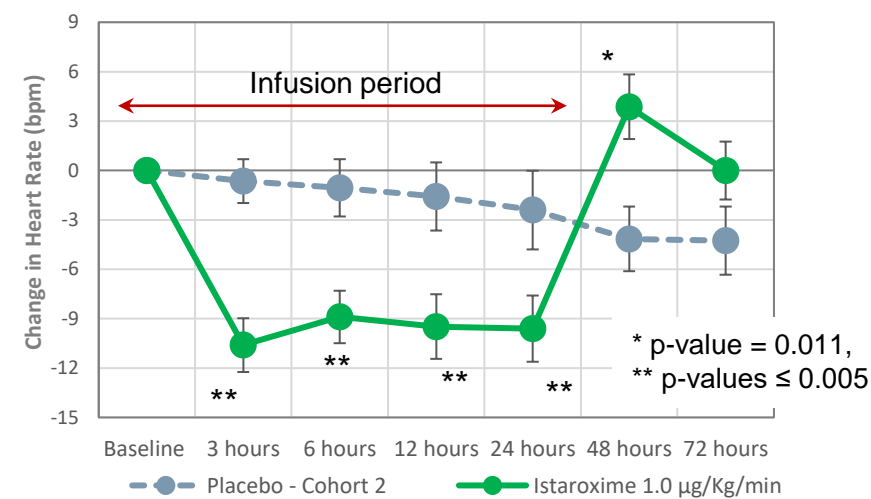
# Heart Rate Decreased and No Increases in Cardiac Troponins

Istaroxime 0.5 µg/kg/min vs. placebo

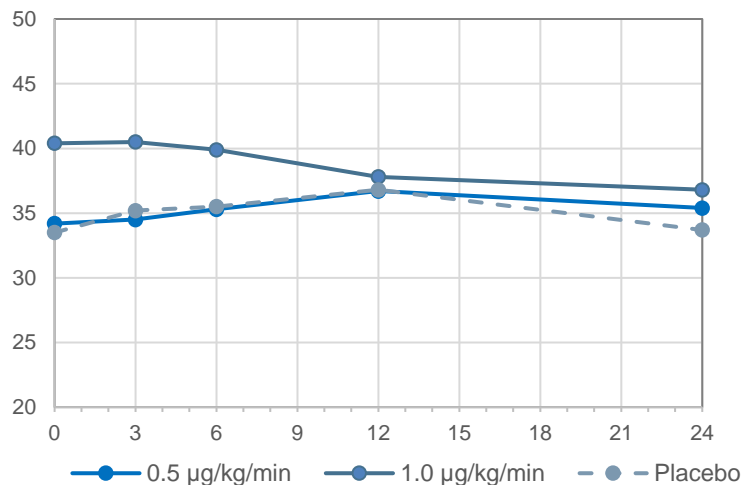


Heart  
Rate

Istaroxime 1.0 µg/kg/min vs. placebo

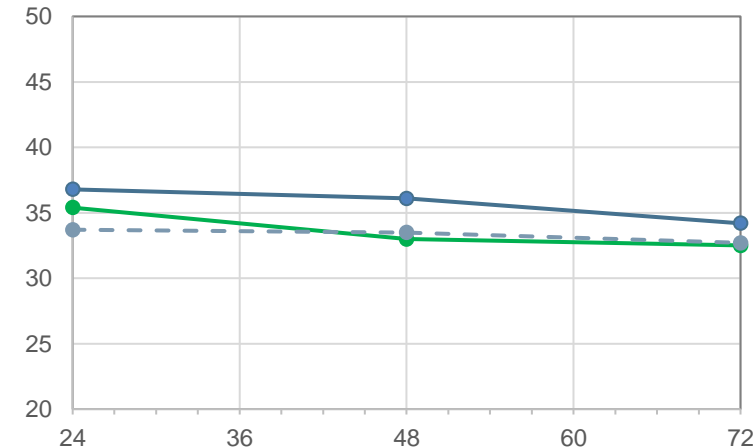


cTnT – 0 to 24 hours



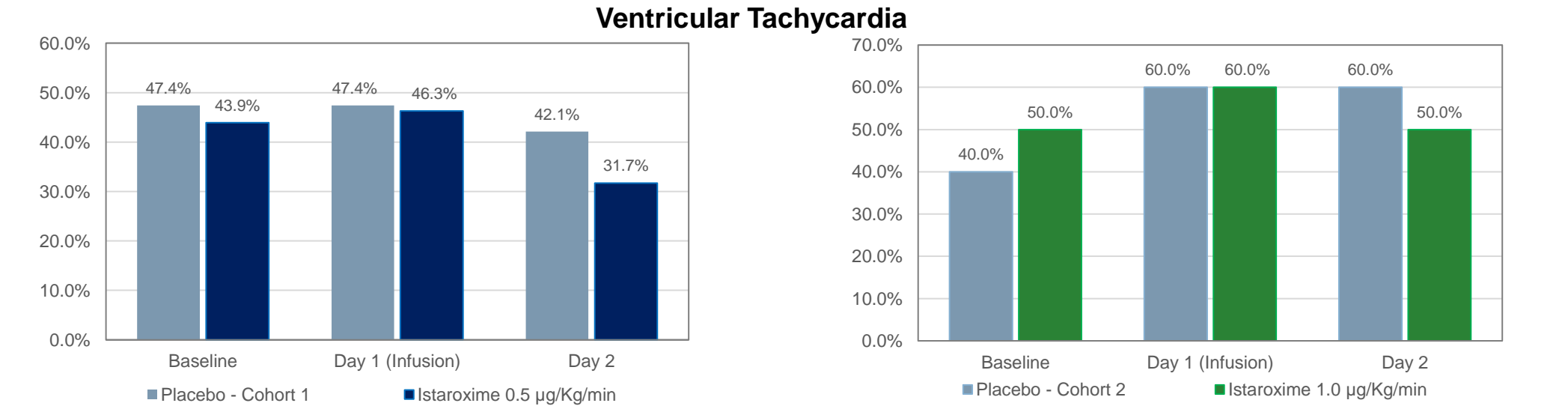
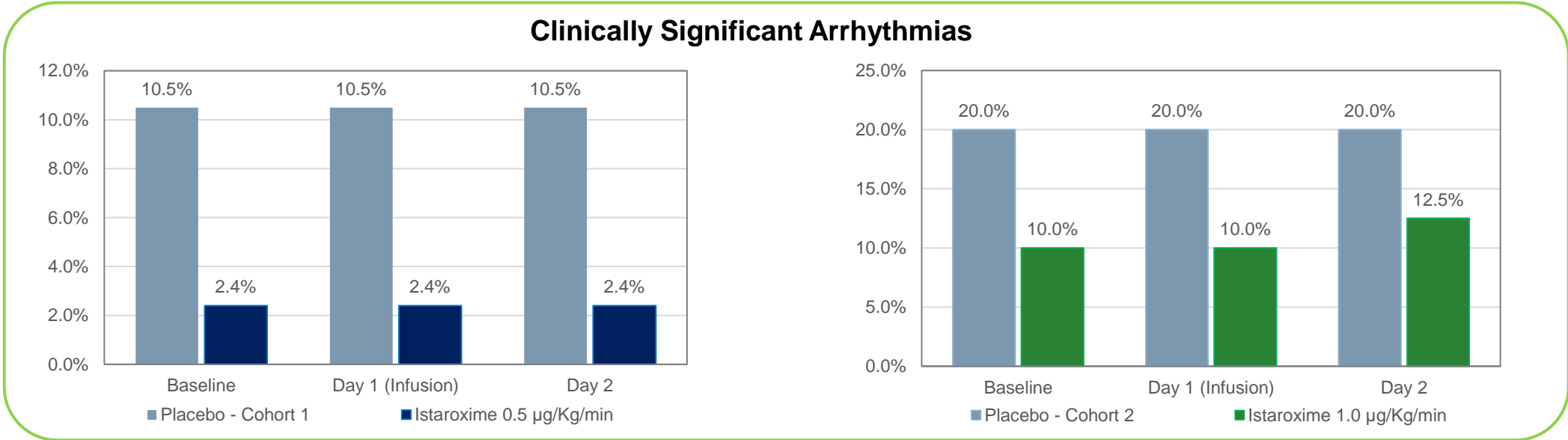
Cardiac  
TnT  
(Myocardial  
Damage)

cTnT – 24 to 72 hours





# Favorable Profile Observed with 24-hour Holter Monitoring



# Istaroxime – Acute Heart Failure

**Objective: Optimize therapy and employ study enrichment strategies to create strong Phase 3 and partnership position**

Execute an additional study designed to complete Phase 2 and inform Phase 3  
- 300 patients, 60 centers globally\*



Enrich therapeutic impact by leveraging characteristics in target population whose needs match the unique attributes of istaroxime: patients with low blood pressure and/or diuretic resistance



Increase infusion time to >24 hours in pursuit of dose optimization



Primary endpoint will again be E/e', but also obtain data on measures that will inform Phase 3 design and pivotal endpoint

Pending adequate funding; ~18 months to execute

# Next Generation, Oral SERCA2a Activators Acute and Chronic Heart Failure Platform

*The Company also has pre-clinical programs on product candidates including:*

## Selective SERCA2a Activators

- **Oral & i.v.** therapies for chronic heart failure (CHF) and AHF
- Attractive approach for **heart failure with preserved ejection fraction (HFpEF)**

## Dual Mechanism, (SERCA2a & Na<sup>+</sup>/K<sup>+</sup>) Compounds

**“Next generation istaroxime” as oral/i.v. for in-patient acute and out-patient chronic use**

**These next generation agents help form complete chronic and acute heart failure treatment portfolio for both licensing/partnership and potential commercialization**

# Summary

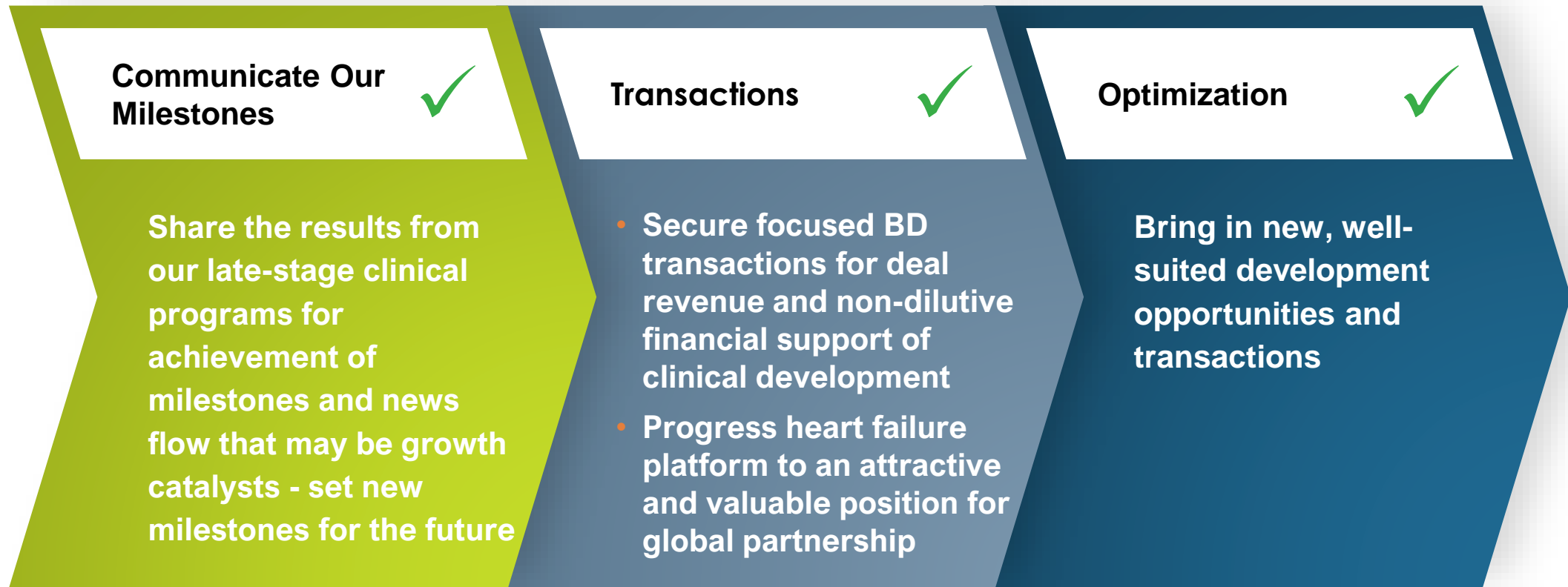
- ✓ Istaroxime has produced positive, differentiating data in three Phase 2 studies for two separate and complementary indications. These markets have significant unmet needs, and no known other late-stage programs in development to address the acute decompensated patient
  - The data is consistent, across all regions/populations and across many endpoints (including many in early cardiogenic shock despite small trial)
- ✓ Istaroxime has demonstrated a highly unique and desirable profile as compared to existing therapies:
  - Improved cardiac function **and** SBP while maintaining renal function and overall safety profile
- ✓ Recent positive Phase 2 study with istaroxime in early cardiogenic shock (ECS) paves the way for what we believe is a relatively fast and less expensive developmental and regulatory pathway
- ✓ The AHF program will proceed with business development (which remains a pre-Phase 3 strategy for istaroxime) and/or additional resourcing while also advancing the next generation, oral SERCA2a activators for chronic and acute HF including HFpEF

# Financial Summary & Capitalization

Cash & Equivalents of ~\$11.4 million as of June 30, 2022

Securities	Common Equivalents as of August 11, 2022
Common Stock	30,627,878
Options (WAEP \$7.84)	4,046,604
Restricted Stock Units	560,900
Warrants (WAEP \$6.64)	16,546,336
Fully Diluted Equivalents	51,781,718

# Strategy for Value Generation



[www.windtreetx.com](http://www.windtreetx.com)





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THERAPEUTICS™

# Appendix



# Istaroxime Unique Opportunity With Attractive Risk / Return Profile

1 Highly consistent results across 3 controlled Phase 2 studies (and 300 patients dosed thus far), in a spectrum of severity and executed in all regions of the world

2 Attractive profile as the only acute heart failure or shock drug that has been shown to significantly improve cardiac function of a failing heart, while rapidly and significantly improving blood pressure, with what so far has been a differentiating safety profile (avoiding many of the use-limiting side effects of existing therapies such as renal, arrhythmias, etc.)

3 Complementary acute CV programs with high unmet need and no active or developing competition

**Istaroxime:  
Attractive Risk,  
Time, Cost and  
Return Profile**

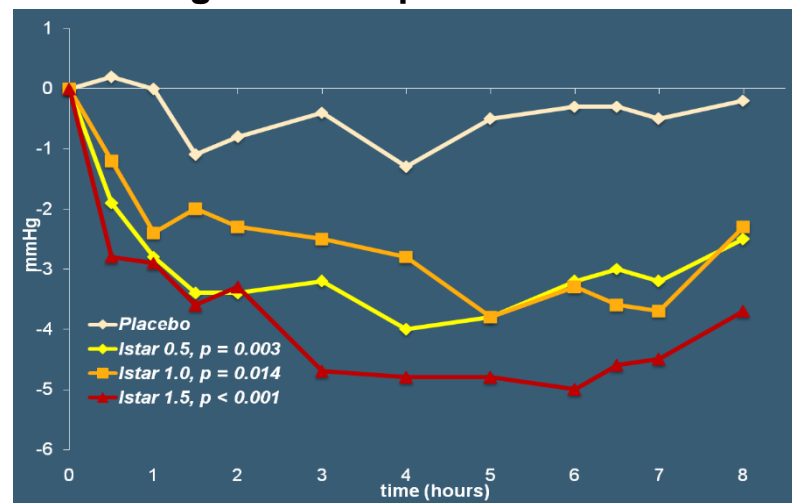
5 Long, successful history of CMC

- 4 Faster and less expensive developmental and regulatory pathway possible
- Attractive pivotal endpoint of blood pressure response is expected to be more straight-forward and better align with a smaller study than one requiring clinical outcome measures.
  - Additionally, istaroxime demonstrated significance in many other benefits that we expect will continue to help us build a strong evidence-based position with dose-optimization and the larger Phase 3 planned for 2023.

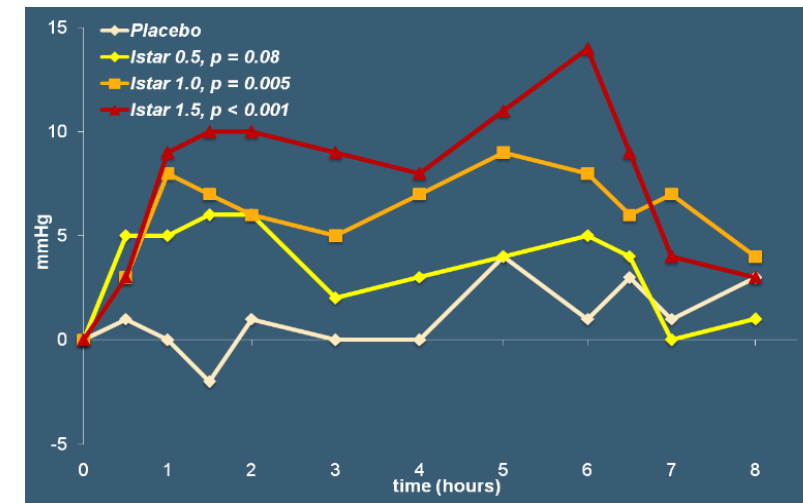
# Istaroxime Phase 2a (HORIZON-HF) Study

- Multicenter, double blind, placebo-controlled, doses 6-hour infusion of istaroxime 0.5, 1.0, 1.5 ug/kg/min, conducted in the EU
- Hospitalized with AHF, with criteria including:
  - LVEF  $\leq 35\%$
  - SBP 90-150 mmHg
- N=120 (30/group)
- Significant improvement in PCWP, SBP, heart rate was lower. Istaroxime was generally well tolerated with no unexpected adverse events

**Primary Endpoint:  
PCWP Significant Improvements**



**Dose-dependent Increase in SBP**



# Istaroxime AHF Phase 2b Adverse Events

Event	Pooled placebo (n=39)	Istaroxime 0.5 mg/Kg/min (n=41)	Istaroxime 1.0 mg/Kg/min (n=40)
<b>All adverse events</b>	23 (59.0%)	31 (75.6%)	33 (82.5%)
<b>Adverse events leading to discontinuation</b>	1 (2.6%)	-	4 (10.0%)
<b>Serious adverse events</b>	2 (5.1%)	2 (4.9%)	6 (15.0%)
Cardiac death	-	-	1 (2.5%)
Cardiogenic shock	-	-	1 (2.5%)*
Cardiac failure	1 (2.6%)	2 (4.9%)	3 (7.5%)
Renal embolism	-	-	1 (2.5%)
Transient ischemic attack	1 (2.6%)	-	-
Hyperventilation	1 (2.6%)	-	-
Hypotension	1 (2.6%)	-	-
<b>Adverse Drug Reaction†</b>	10 (25.6%)	23 (56.1%)	25 (62.5%)
<b>Cardiovascular††</b>	<b>9 (23.1%)</b>	<b>4 (9.8%)</b>	<b>7 (17.5%)</b>
Gastrointestinal‡	2 (5.1%)	4 (9.8%)	14 (35.0%)
Infusion site pain/inflammation	-	20 (48.8%)	13 (32.5%)

Note: data shown as n° patients (%) - patients can have more than one event during the 30-day follow up period

\* Same patient who then died, and 1 additional death occurred at Day 31 (cardiac death) outside the 30 day window

† Adverse Drug Reactions are AEs related to study drug

†† Most common - arrhythmia, atrial fibrillation, cardiac failure, ventricular tachycardia

‡ Most common - abdominal pain, nausea, vomiting, diarrhoea

# SEISMiC: Serious Adverse Events and Adverse Drug Reactions

Event	Istaroxime (N=29)	Placebo (N=31)
<b>All adverse events</b>	27 (93%)	25 (81%)
<b>Serious adverse events</b>	6 (21%)	6 (19%)
Cardiac arrest	1 (3%)	0
Cardiac failure	2 (7%)	2 (6%)
Cardiac failure acute	0	1 (3%)
Cardiac ventricular thrombosis	0	1 (3%)
Cardiac artery stenosis	0	1 (3%)
Ventricular fibrillation	1 (3%)	0
Ventricular tachycardia	1 (3%)	0
Coronavirus infection	0	1 (3%)
Pneumonia	1 (3%)	0
Acute kidney injury	1 (3%)	0
<b>Adverse drug reaction†</b>	15 (52%)	3 (10%)
Gastrointestinal‡	9 (31%)	2 (6%)
Infusion site pain/inflammation	4 (14%)	1 (3%)

# SEISMIC: Safety and Efficacy Appeared More Favorable with the 1.0 vs 1.5 µg/kg/min and Placebo

***1.0 µg/kg/min dosing was associated with:***

- **Early SBP increase and improvement in more echocardiographic parameters of cardiac function**
- **More favorable adverse event, serious adverse event and clinical event profile**

Clinical Events by Dose	Statistic	Placebo (N=31)	Istaroxime 1.0 µg/kg/min (N=16)	Istaroxime 1.5 µg/kg/min (N=13)
SBP AUC 0-24hrs	LS-Means (SE)*	209.9 (27.38)	282.7 (35.79)	304.1 (44.11)
Worsening HF through 96-hours	No. events	1 (3%)	0 (0%)	5 (38%)
Heart Failure Readmissions through 30-days	No. events	3 (12.9%)	0 (0%)	0 (0%)
Length in ICCU/CCU, days [c]	Mean (SD)	4.55 (2.23)	3.50 (1.41)	6.38 (4.46)
All-Cause Mortality through 30-Days	No. events (%)	1 ( 3%)	1 ( 6%)	3 (23%)
All-Cause mortality or HF readmission through 30-days	No. events (%)	4 (12%)	1 (6%)	3 (23%)

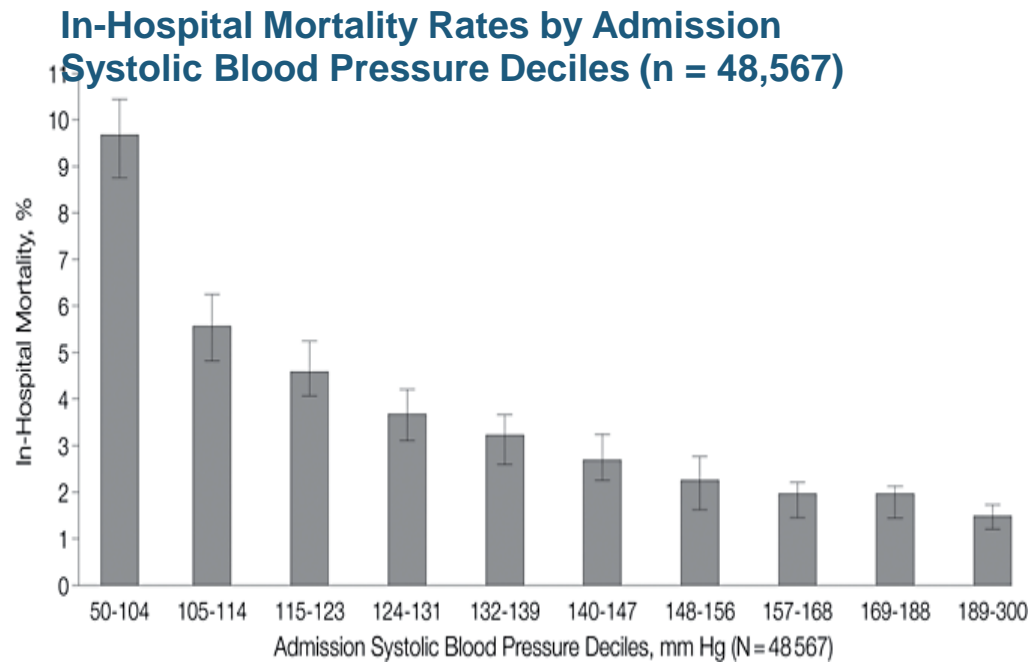




# Acute Heart Failure

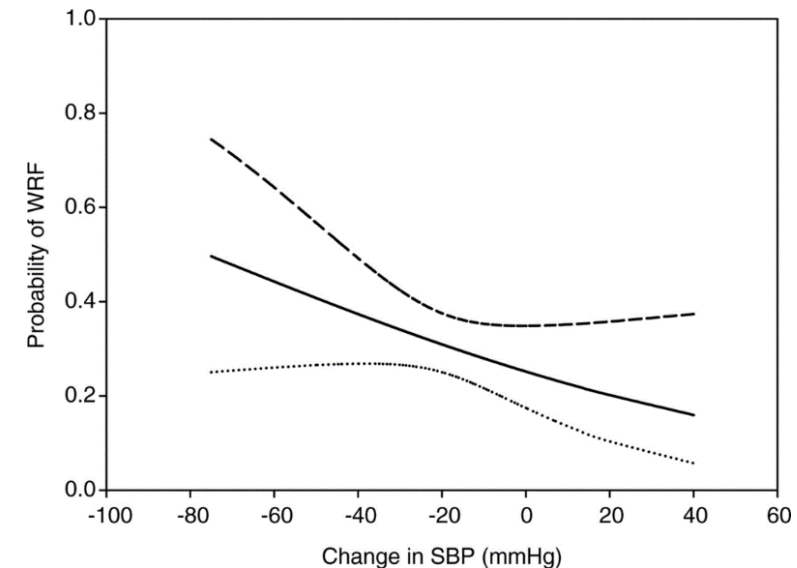
## Significant Healthcare Issue with Significant Unmet Clinical Need

- Patients with low blood pressure (SBP) and peripheral hypoperfusion are high risk, challenging patients. These patients are also generally resistant to diuretic therapy and often discharged in a sub-optimal state.
  - Low SBP in-patient mortality approximately two-fold greater than normal/high SBP<sup>1</sup>
  - There is a direct relationship between early drop in SBP and worsening renal function in acute heart failure<sup>2</sup>



Gheorghiade, M. et al. JAMA 2006;296:2217-2226.

## Early drop in systolic blood pressure and worsening renal function in Acute Heart Failure: renal results of Pre-RELAX-AHF Study



Voors, A. et al. European Journal of Heart Failure 2011; 13; 961-967