Windtree Therapeutics
Company Overview

April 2024

Nasdaq: WINT

WINDTREE THERAPEUTICS™

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 Company’s most recent reports on Form 10-K, and any subsequent quarterly reports on Form 10-Q and current reports on 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.

Under no circumstances shall this presentation be construed as an offer to sell or as a solicitation of an offer to buy any of the Company's securities. In addition, the information presented in this deck is qualified in its entirety by the Company Filings. The reader should refer to the Company Filings for a fuller discussion of the matters presented here.

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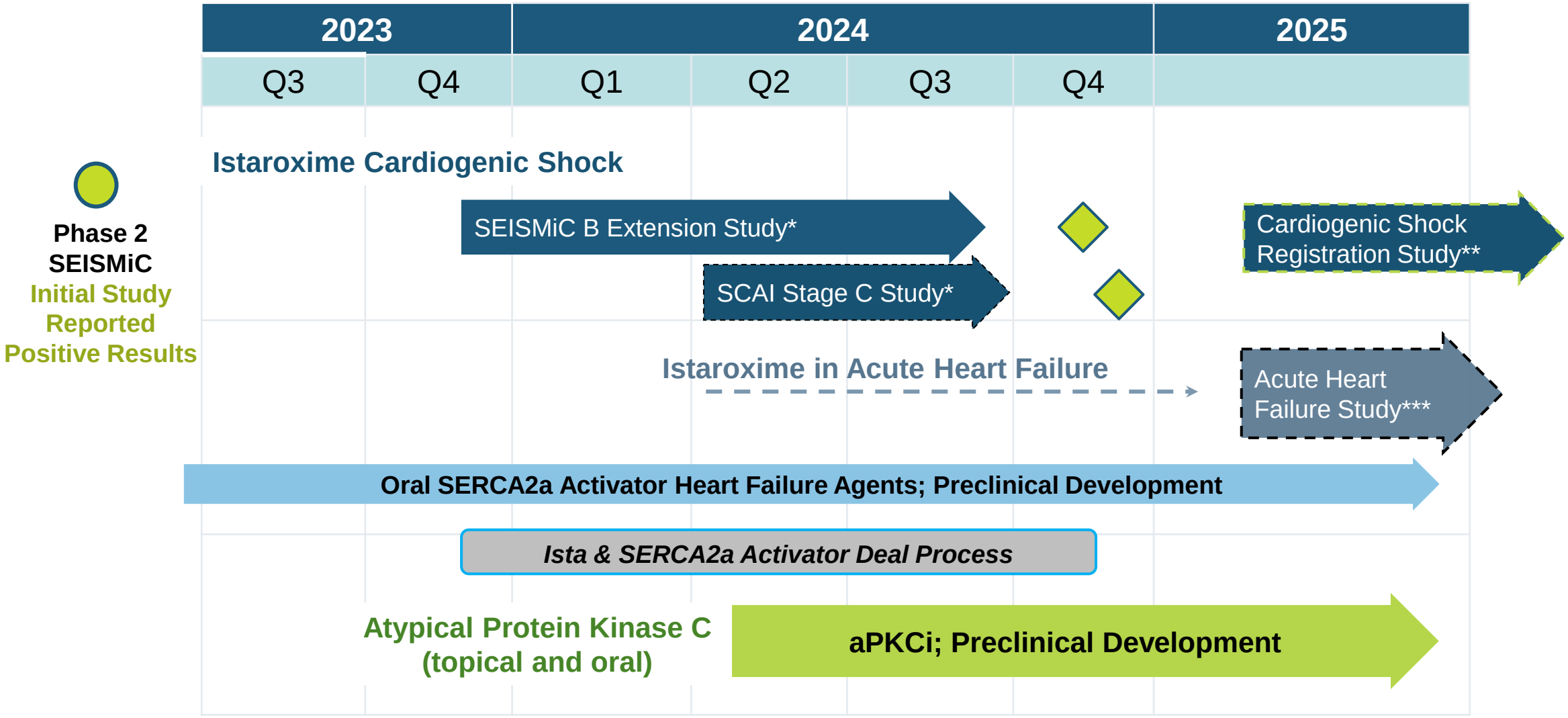
Windtree Investment Highlights

- Biopharmaceutical company focused on oncology and cardiovascular 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 compared to currently available rescue medications in three Phase 2 global studies, highlighted by improvements in cardiac function and increases in blood pressure with favorable renal function profile
- Istaroxime is in Phase 2b clinical development for cardiogenic shock and acute heart failure; platform also includes next generation oral, SERCA2a activators in preclinical development
- 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
- Global and regional license deals in place with a priority focus on potential additional global license or strategic transaction with new partner for cardiovascular assets
- Lean, capital efficient operation led by a highly experienced management team in oncology and cardiovascular development, deals and commercialization

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**	• **Positive Phase 2 study** • **Executing small follow-on studies intended to transition to Phase 3**
Istaroxime	Acute Heart Failure	Phase 2b	• Positive Phase 2a and 2b data • Augment AHF data with cardiogenic shock data, if positive and adequate, for Phase 3 for AHF with partnership • 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	• 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	• **IND enabling studies**
Rostafuroxin	Treatment Resistant Hypertension – Genotypically identified patients	Phase 2b	• 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	• **Global out-license in place** • Partner responsible for all costs of development

Milestone Strategy for Value Creation



* Study and guidance depends upon adequate funding or partnership
** Study and guidance pending positive EOP2 meeting and adequate funding
*** Study and guidance pending positive EOP2 meeting and adequate funding (via partnership)

◆ Represents planned data available

Istaroxime

Cardiogenic Shock

Potential to transform the standard of care for critical patients

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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.**

- Caused by severe impairment of cardiac function that results in diminished cardiac output, end-organ hypoperfusion and hypoxemia
- 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 survivors[1]
- US + EU markets represent an ~$1.0B market potential[2] with high unmet need

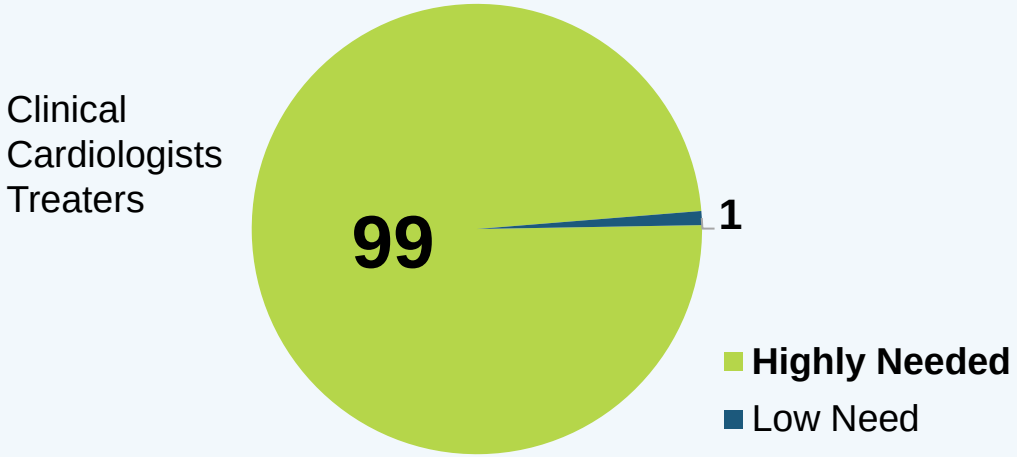
1) Burgos, JSCAI (1) 2021Kolte D, American Heart Association; 2014 Jan 13; (rates associated with classic, stage C shock)
2) Estimates from claims data and epi data September 2021, multiplied by assumed various regional prices

Significant Unmet Need and Reported Desire for Istaroxime

- **No 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”
- A therapy that can be used **earlier** to rapidly **improve blood pressure and cardiac function without unwanted side effects** is needed

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 ECS[1]***



✓ **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

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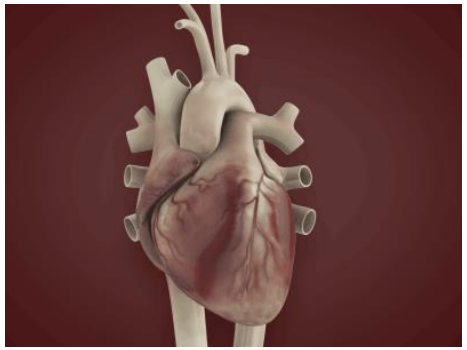
1) Market research conducted by Sermo, a leading provider of real time physician insights

Istaroxime – Novel First-in-Class Therapy

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

Dual Mechanism of Action



1 **Increases the Force of Contraction**
via inhibition of the sodium-potassium pump and effects on the sodium-calcium exchanger

2 **Improves Cardiac Relaxation**
via stimulation of SERCA2a activity which enhances calcium reuptake

Impact on both systolic (contraction) and diastolic (relaxation) dysfunction

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Istaroxime Cardiogenic Shock Program Came from AHF Phase 2 Trials and the Potential Attractive Regulatory Pathway

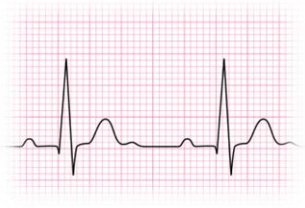
In Phase 2a and 2b data in AHF istaroxime demonstrated:

Cardiac Function Improved with Both Doses

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

Increased in Systolic Blood Pressure

Increased Renal Function (eGFR)



Heart Rate Decreased

Favorable Heart Rhythm Profile Observed

- No increase in clinically significant arrythmias or ventricular tachycardia

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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 75-90 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 in the first group and 1.0 µg/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

Positive Results in the Early Cardiogenic Shock Study

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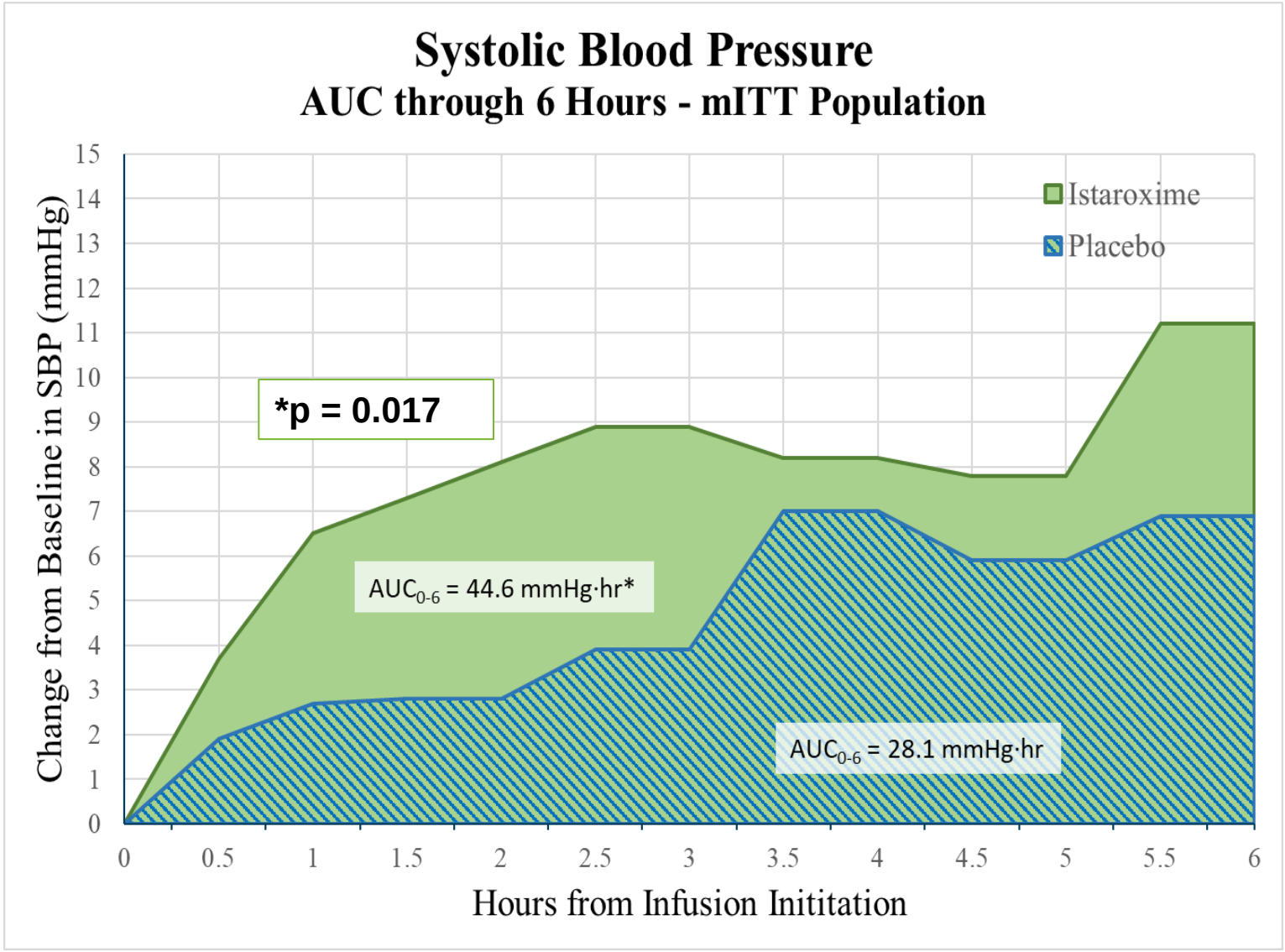
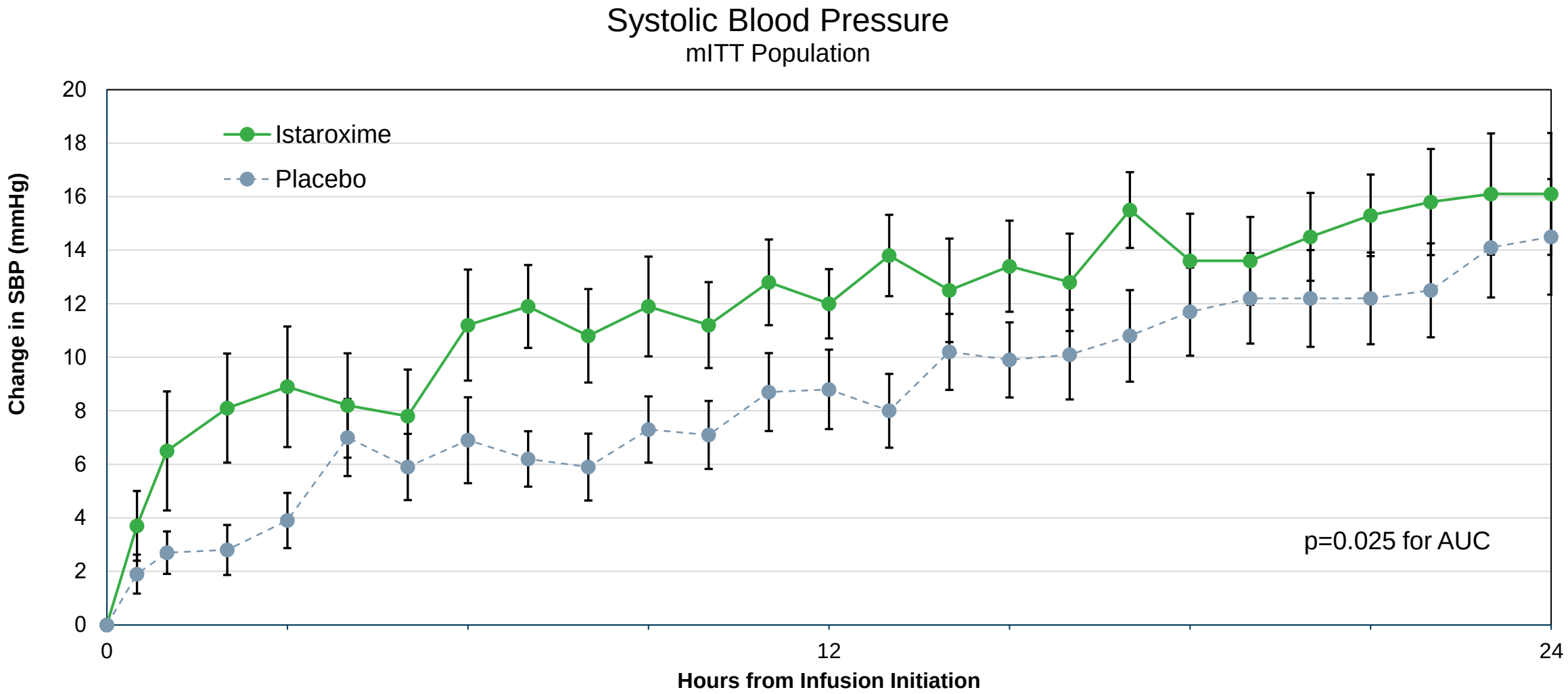
Istaroxime Achieved Positive Primary Endpoint



Systolic BP Improvements Persisted over 24 Hours



Cardiac Function Improvement

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

- ✓ **Cardiac index (amount of output from the heart over a minute) significantly increased**
- ✓ **Stroke volume (amount of blood from the heart with each heartbeat) substantially increased**
  - (4 mL/m^2) approaching statistical significance
- ✓ **The strength and cardiac geometry of the heart improved including:**
  - Left atrial area was reduced
  - Left ventricular end systolic volume was reduced
  - Left ventricular end diastolic volume was reduced

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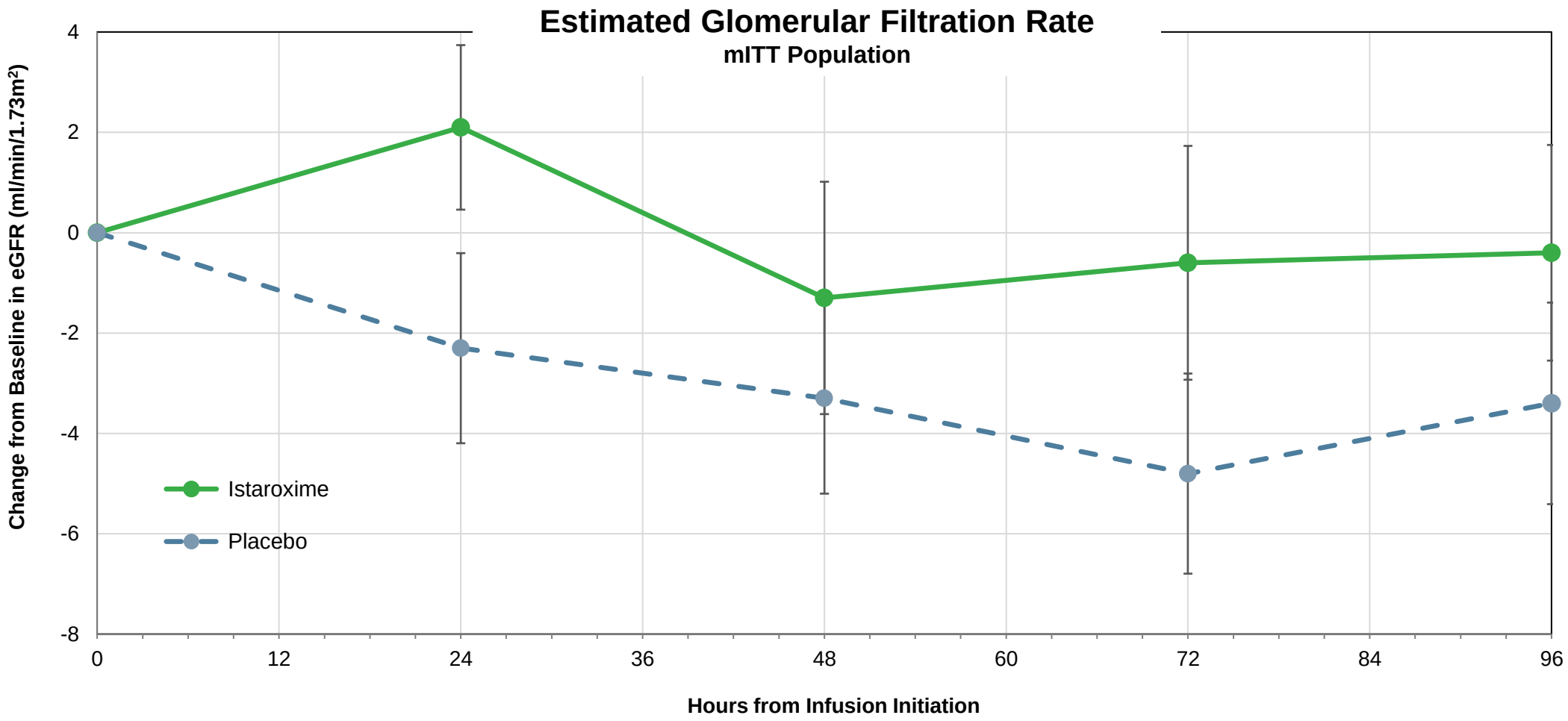
Treatment was Associated with a Favorable Renal Profile

Renal function was not decreased in istaroxime treated patients

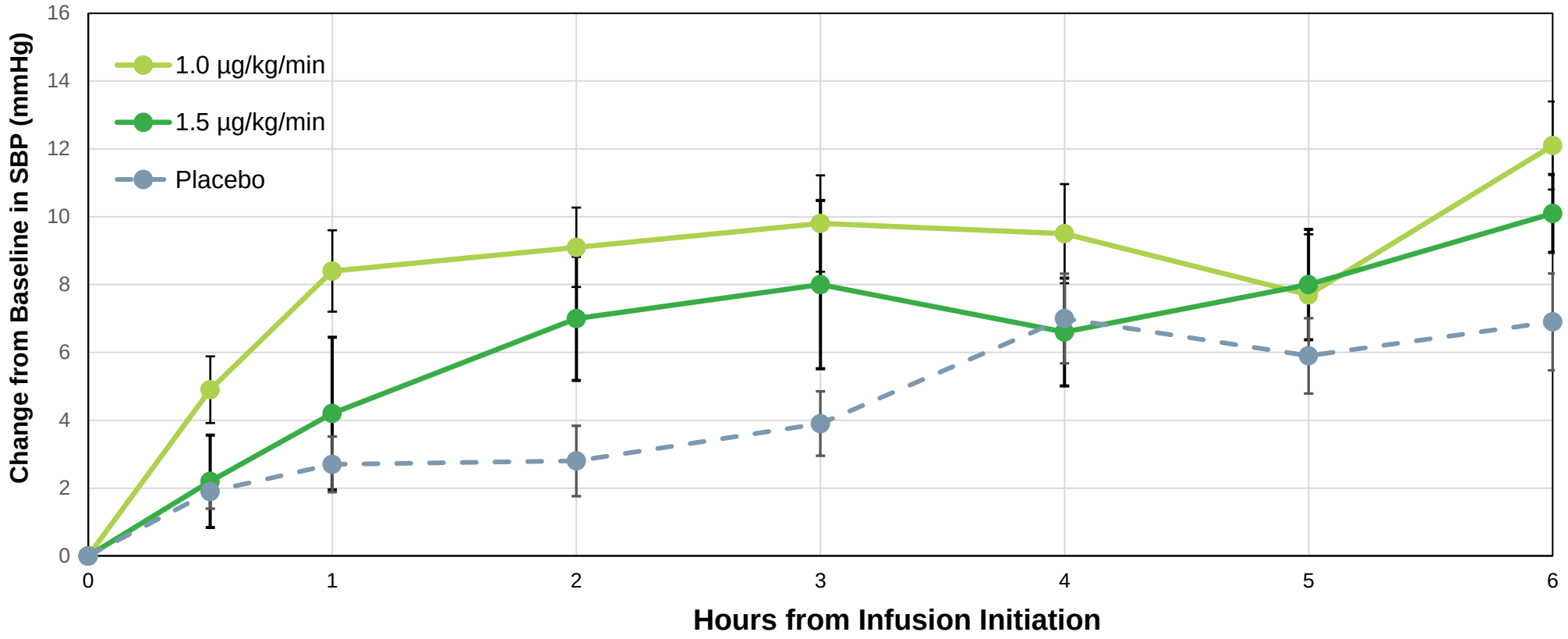


Data shown as means and standard errors

1.0 µg/kg/min Produced a Favorable Effect on SBP

1.0 µg/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



All Subjects (n=60)

SEISMiC Study Results Summary

- ✓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 align with the existing data from the program in AHF

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Cardiogenic Shock Development Strategy

Focus on thoroughness, speed and relatively low cost of trials

SEISMiC Study

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

Expected Steps to Phase 3 Readiness

SEISMiC Extension 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.

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

Cardiogenic Shock Represents a Significant Opportunity for Istaroxime and Windtree

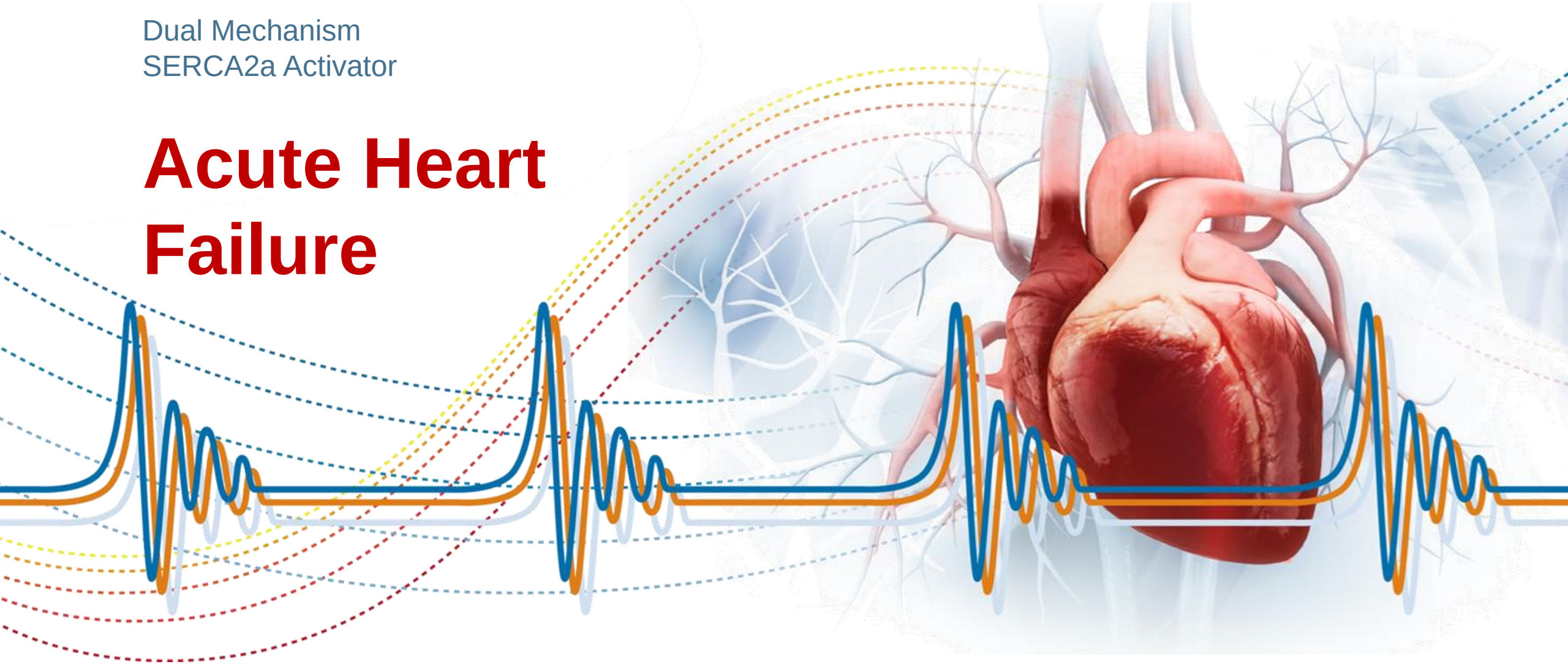
- Significant opportunity for Istaroxime to make a difference:
  - ~20-30% mortality in classic shock and high morbidity
  - Very long average length of hospital stay (~ 19.5 days[1]) means high cost of hospital care (estimated >$175k[2]) and creates opportunity for pharmacoeconomic benefits
- Currently 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

Istaroxime

Dual Mechanism
SERCA2a Activator

Acute Heart Failure



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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

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Sources: American Heart Association; DRG Data

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

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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

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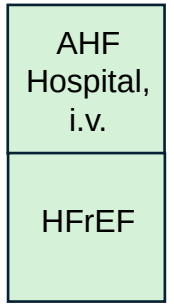
Next Generation, Oral SERCA2a Activators Platform has Potential for *both Major* Types of HF in Acute *and* Chronic Therapy

Today:

Istaroxime

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

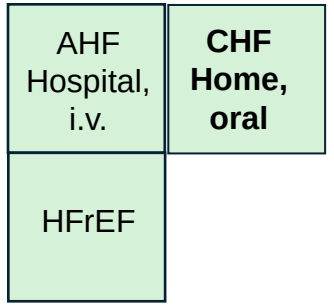
Development Strategy:



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**



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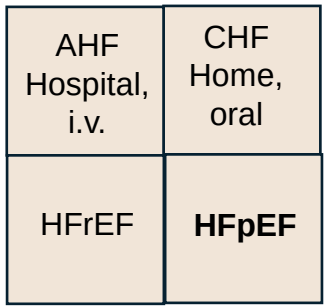
Preclinical Pure SERCA2a Activators

- **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



Atypical Protein Kinase C iota (aPKCi) Inhibitors

Potential Multiple Tumor Types

Innovative topical and oral formulations

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Oncology Assets: aPKCi Topical (VAR-101) and Oral (VAR-102)

Newly acquired, first in class atypical protein kinase C iota inhibitors (aPKCi)

✓ **Novel, emerging oncogenic target**

- Protein kinase inhibitors are a class of anti-cancer therapeutics that have made a significant impact on the treatment of cancers.
- aPKCi is a promising atypical PKC iota isozyme with defined oncogenic role in multiple signaling pathways, and in the initiation and development of multiple tumor types
- aPKCi inhibitors represent a next generation of Hedgehog (Hh) pathway inhibitors targeting the most downstream component of the pathway and are fundamental components of the Hh resistance pathway

✓ **Advanced preclinical studies with early promising signals**

- The active pharmaceutical ingredient has demonstrated dose responsive characteristics in murine and human basal cell carcinoma (BCC) cell lines, as well as non-small cell lung cancer (NSCLC) mice models
- Initial ADME studies (in rat dog, primate), kinase selectivity/potency, and protein binding studies have been done as have skin permeation studies of the active pharmaceutical ingredient

✓ **Multiple clinical development opportunities**- Specific, potent approach with a topical formulation for cutaneous cancers (i.e. BCC, Gorlin Syndrome, CTCL, etc.) and oral formulation to focus on broader tumor types as monotherapy or in combination

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Source: Windtree Data on File

Oncology Assets: aPKCi inhibitor Topical and Oral

Next Steps

- ✓ **Progress the IND-enabling activities including pre-IND meeting, toxicology (including topical)**
- ✓ **Create a comprehensive clinical and CMC development plan that leverages the assets' unique characteristics and mechanisms of action on the highest unmet disease needs**

- Decide on **leading with rare disease** option such as Gorlin Syndrome **vs. more prevalent tumor type** such as Basal Cell Carcinoma
- Ensure differentiation and **maximizing benefit vs. risk / toxicity as a key evaluation element**. For example, focus on **topical formulation** as a potential way to optimize benefit, minimize toxicity, treat earlier and improve patient compliance compared to systemic treatment options
- Fully identify and **rigorously assess various opportunities across tumor types** with the Scientific Advisory Committee where the mechanism is important, there are preclinical data signals and clinically feasible pathway to registration and commercialization.

Matching Preclinical Data, Attributes, Scientific Rationale and Market Opportunities for Optimal Development Path

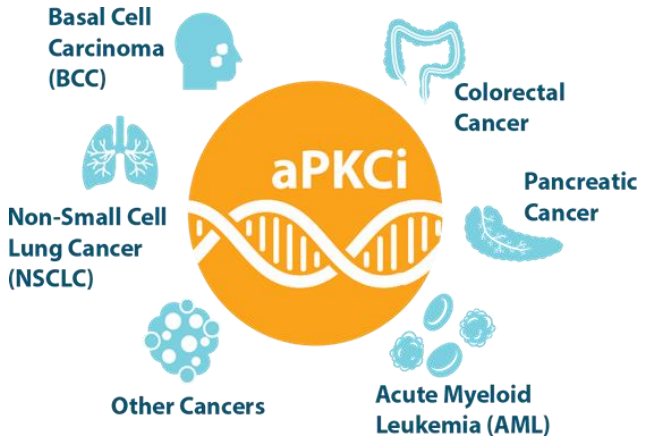
Early Observations of the Key Attributes of Active Pharmaceutical Agent	
Rational Design	✓Molecules designed through med chem, SAR, and in vitro and in vivo testing
Selectivity	✓High degree of kinome selectivity
Biomarker Activity	✓There is potential for a biomarker-driven approach targeting aPKCi/Gli-1/K-RAS positive tumors
Potential for Less Resistance	✓aPKCi is a potential GLI regulator; upregulation of GLI occurs in resistance
PK	✓Preliminary PK and ADME characterization has been done in rodent, dog and primates. Tolerability has been good in these studies
Therapeutic Index	✓Dose dependent potential and potential biomarker activity observed across *in vitro* murine and human BCC cells lines and in explanted human BCC cells from Moh's sections

Cutaneous Malignancies (lead)

- Assessment may include Basal Cell Carcinoma (BCC), Gorlin Syndrome, Cutaneous T-Cell Lymphoma (CTCL), etc.

Oral, Systemic Treatment Tumors

- Assessment may include Non-Small Cell Lung (NSCL), Pancreatic, Colorectal, Ovarian, Acute Myeloid Leukemia (AML)



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Source: Windtree Data on File

Windtree Strategy for Value Creation – Deliver Data and Deals

2024 Focus and Planned Deliverables

- ✓ Interim and final data from istaroxime extension study in Cardiogenic Shock (CS)
- ✓ Data on istaroxime in Stage C CS
- ✓ Support partner (Lee's) start up activities for phase 3 Acute Heart Failure study
- ✓ Secure a global license for istaroxime and SERCA2a activators
- ✓ aPKCi inhibitor IND-enabling studies
- ✓ Explore additional acquisition and/or strategic transactions
- ✓ Drive capital efficacy with further material-level burn cuts and partnerships

Execute smart, rigorous development, generate data and create opportunities

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 Deals

- **Highly engaged BD activity for global (ex-Greater China) license for Istaroxime, SERCA2a Activators**
- **Opportunities for newly acquired oncology assets**

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Financial Summary

Cash

December 31, 2023	$4.3M

✓ Driving Capital Efficiency to Program Investment

- In 2023, significantly reduced company expenses and cash burn (28%) via out-licensing KL4 platform, focusing resources on istaroxime lead priority program
- Plans for 2024 include further significant cash burn reductions to be achieved via potential out-license of capital-intensive, late stage istaroxime program and the company shifting focus to preclinical programs

Securities	Est. Common Stock Equivalents* as of April 22, 2024
Common Stock	510,179
Warrants (WAEP $279.07)	258,130
Options (WAEP $1,663.38)	15,400
Restricted Stock Units	8,040
Fully Diluted Equivalents	791,749

* Estimated based on respective number outstanding on April 19, 2024 with a 1-for-18 reverse split ratio applied.