Windtree Therapeutics

Early Cardiogenic Shock Investor Call

May 23, 2022

(NASDAQ: WINT)

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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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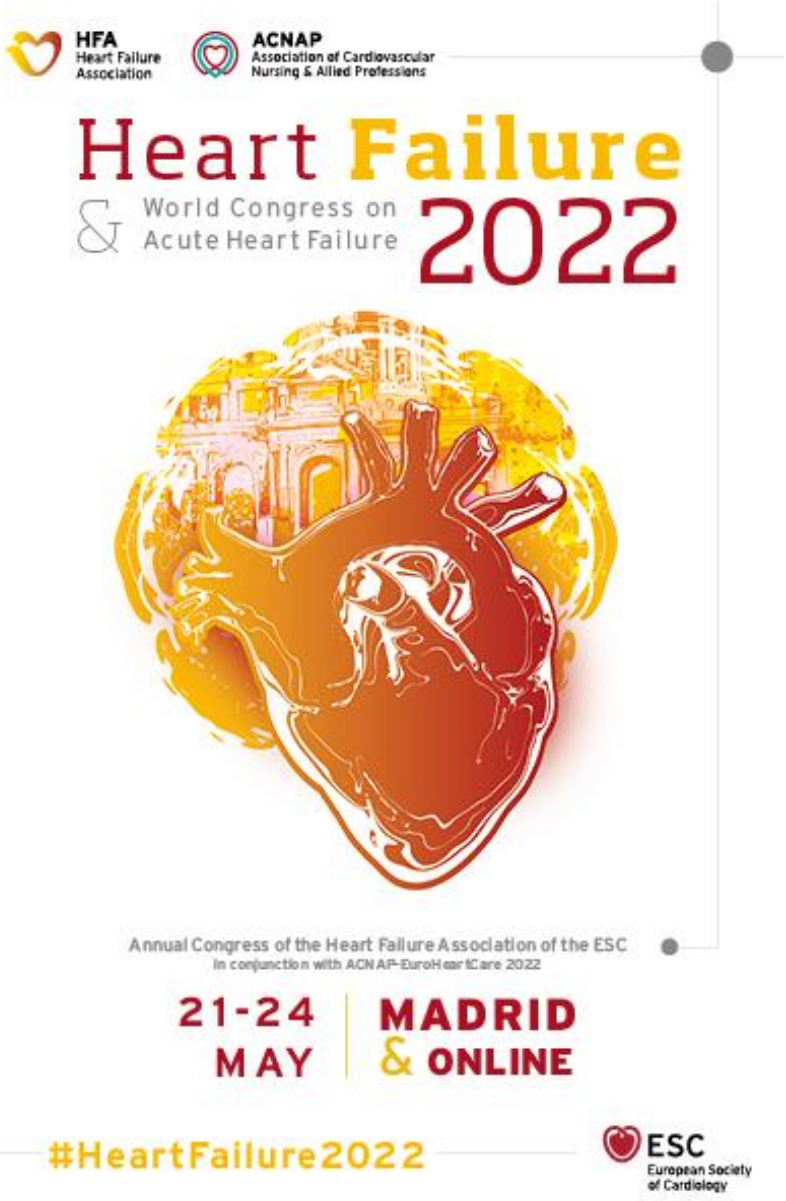
Istaroxime Early Cardiogenic Shock Update:
Live From ESC Heart Failure, Madrid Spain

Istaroxime early cardiogenic shock data from our SEISMiC Phase 2 study was presented at a late-breaker session earlier today here at the ESC Heart Failure meeting:

"The safety and efficacy of istaroxime for PreCardiogenic Shock"

Speaker: Marco Metra, MD (University of Brescia – Brescia, Italy)



Istaroxime – Novel First-in-Class Therapy

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

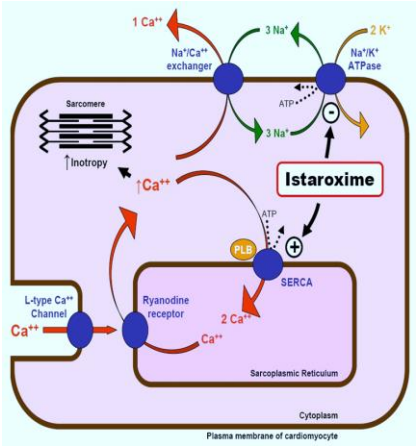
Dual Mechanism of Action

1 Inhibition of the sodium-potassium pump and effects on the sodium-calcium exchanger results in increased contraction

Istaroxime

2 Stimulation of SERCA2a activity enhances calcium reuptake resulting in improvement of the diastolic relaxation (greater fill volume) and subsequent contraction cycle

Impact on both systolic and diastolic dysfunction



Istaroxime AHF Phase 2a & 2b Studies – Summary

Multicenter, double blind, placebo-controlled, parallel group in 240 patients

Phase 2a	n=**120** ADHF Patients	Dosing= **0.5, 1, 1.5** µg/kg/min	**6** hour Infusion
Phase 2b	n=**120** ADHF Patients (dyspnea plus need for IV furosemide ≥ 40mg)	Dosing= **0.5, 1.0** µg/kg/min	**24** hour Infusion

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

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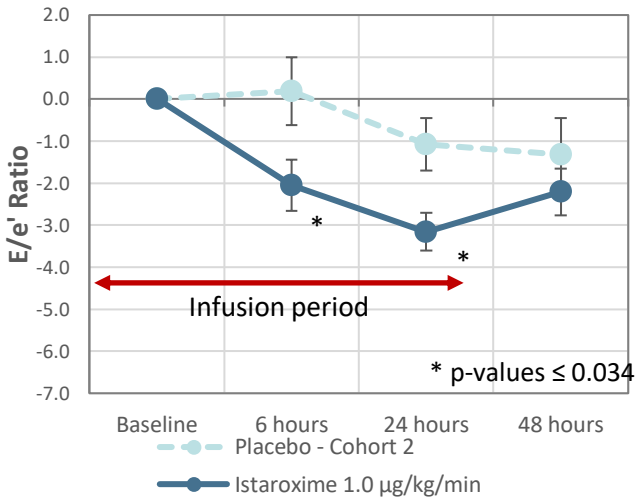
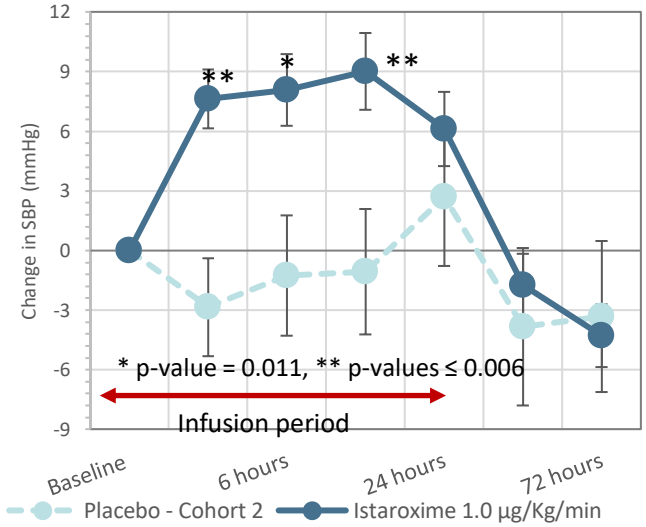
Acute Heart Failure Phase 2b

Significant Improvements in E/e', Stroke Volume and Blood Pressure along with a Favorable Renal Profile

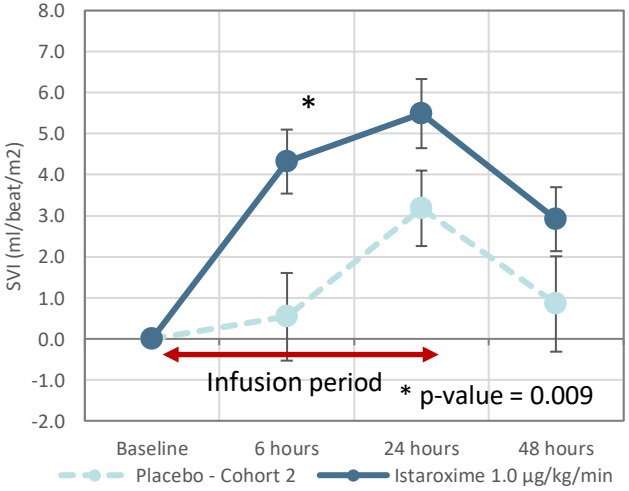
E/e’



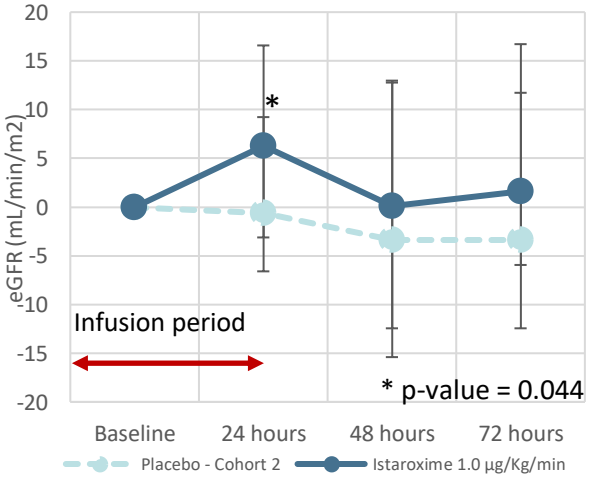
Systolic Blood Pressure (SBP)



Stroke Volume



GFR (Renal Function)



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1) E/e’ echocardiographic assessment of PCWP; Note: Data shown as means and standard errors

SEISMiC Study

Istaroxime in Early Cardiogenic Shock

Additional potential indication in active clinical development

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Cardiogenic Shock

Cardiogenic shock is a **severe presentation of heart failure** characterized by **very low blood pressure and hypoperfusion** accompanied by high PCWP and decreased urine output

- 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[1]
- Represents an approximate $1.25B total market potential[2]

1) Kolte D, American Heart Association; 2014 Jan 13
2) Estimates from claims data and epi data September 2021, multiplied by assumed various regional prices

Early Cardiogenic Shock Treatment

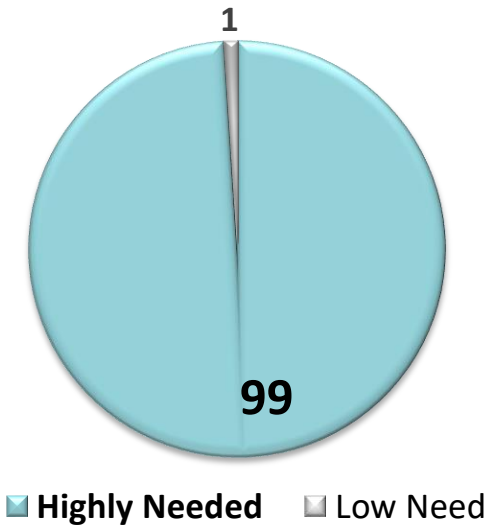
Istaroxime Potential Opportunity to Address Significant Unmet Need

- **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**

Market Research[1]

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

Clinical Cardiologists Treaters



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

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

Early Cardiogenic Shock Treatment

Istaroxime Potential Opportunity for Accelerated Pathway

FDA Regulatory Commentary and Precedent

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**[1]
(Precedent: NDA for 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)[2]

Precedent indicates potential accelerated regulatory pathway and review opportunities

Potential for a complementary program that may have a scale which is faster and less expensive than the fundamental, larger AHF development program

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1) Kosaraju A, Hai O. Cardiogenic Shock. [Updated 2019 Jan 25]. In: https://www.ncbi.nlm.nih.gov/books/NBK482255/ CSRC Think Tank - July 24, 2019
2) Senatore et al., Am J Cardiovasc Drugs, February 2019, Volume 19, Issue 1, pp 11–20 (https://doi.org/10.1007/s40256-018-0297-9)

SEISMiC Early Cardiogenic Shock Study

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, 1.5µg/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

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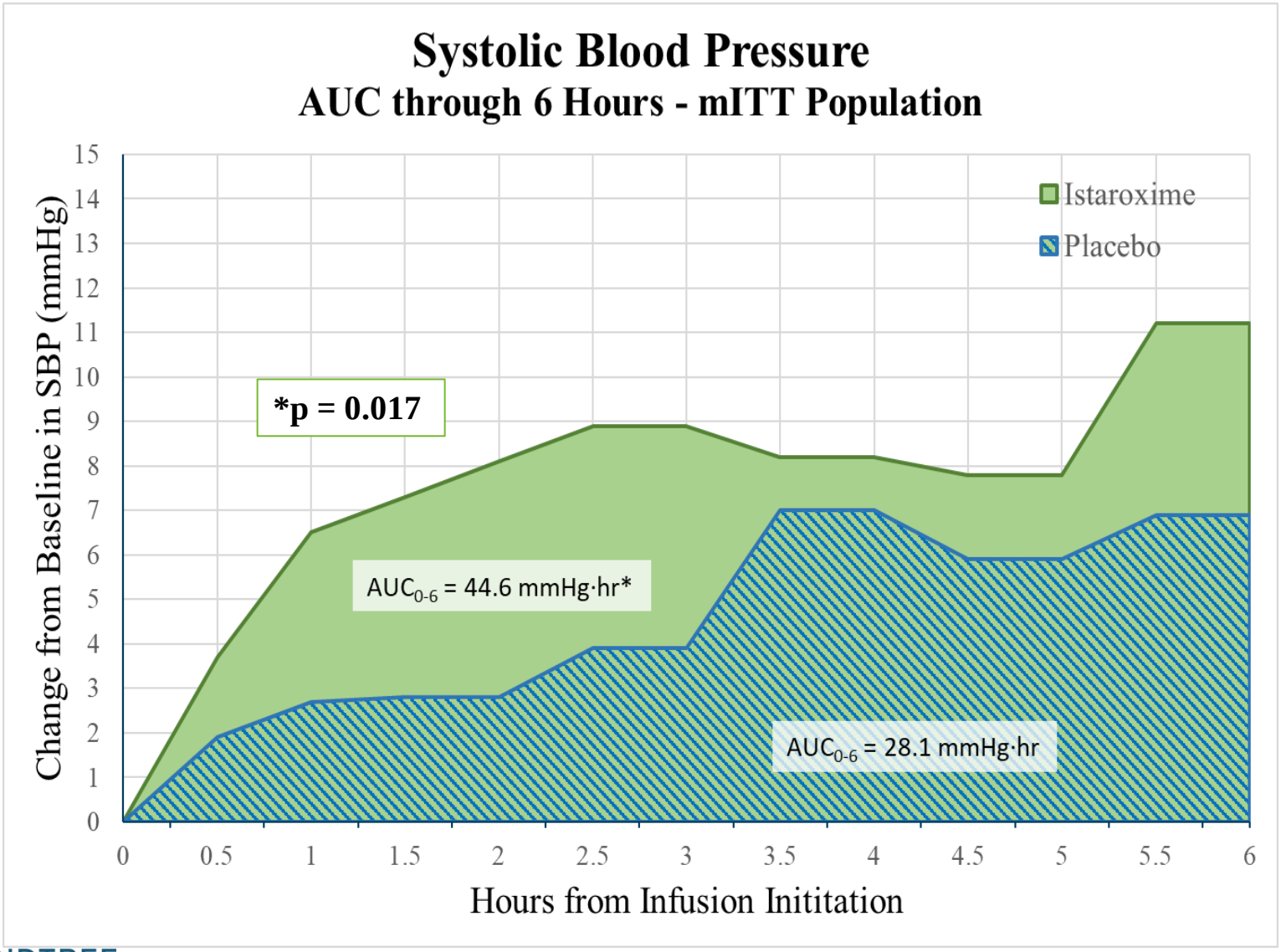
SEISMiC Results Summary

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)
- Key secondary endpoints of systolic and diastolic cardiac function and performance were significantly 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 treatment for AHF as well as enable us to continue to progress the program in cardiogenic shock

Primary Endpoint – Difference in SBP Profile



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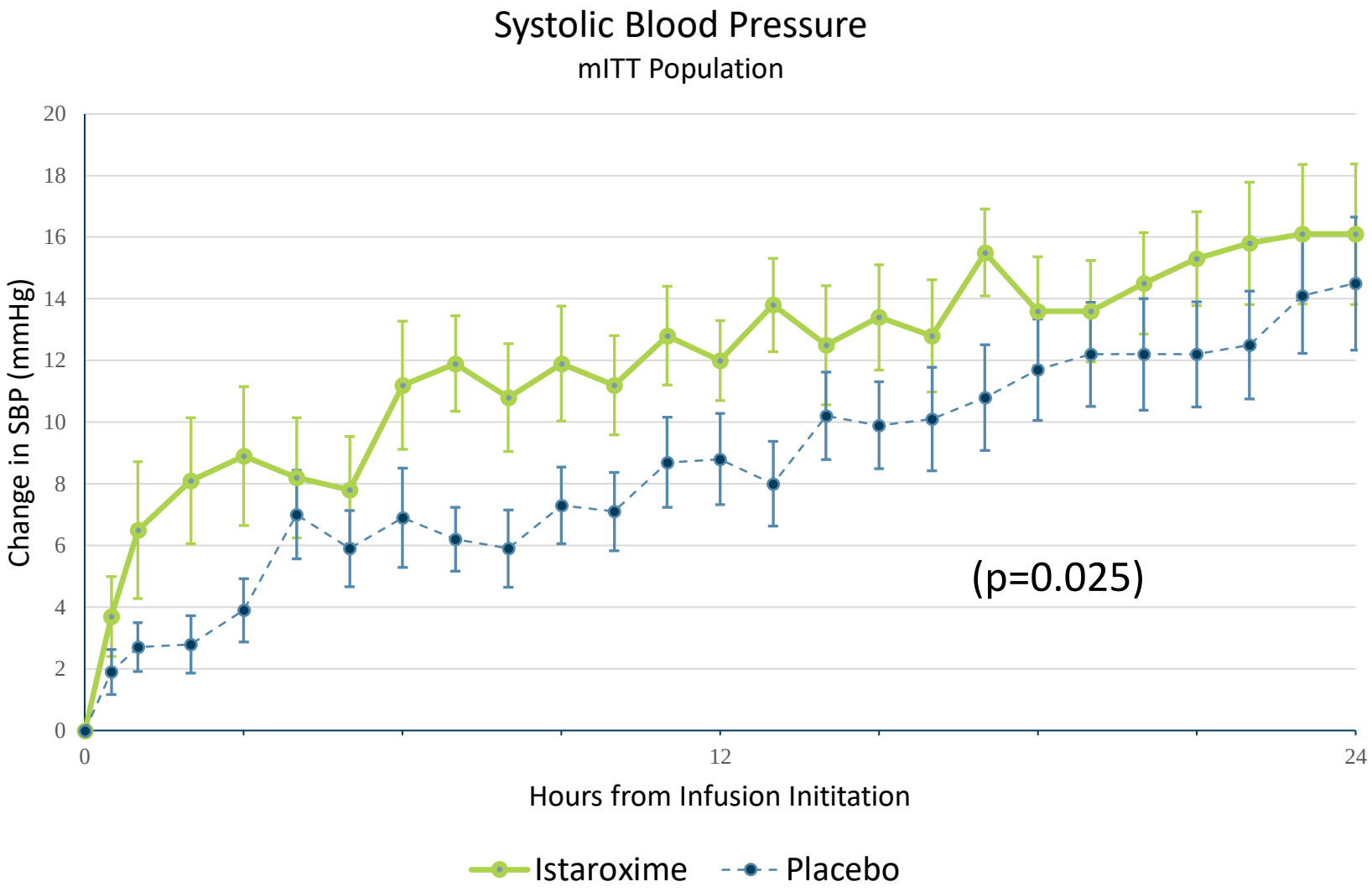
Secondary Results -
Systolic BP Improvements Persisted over 24 Hours



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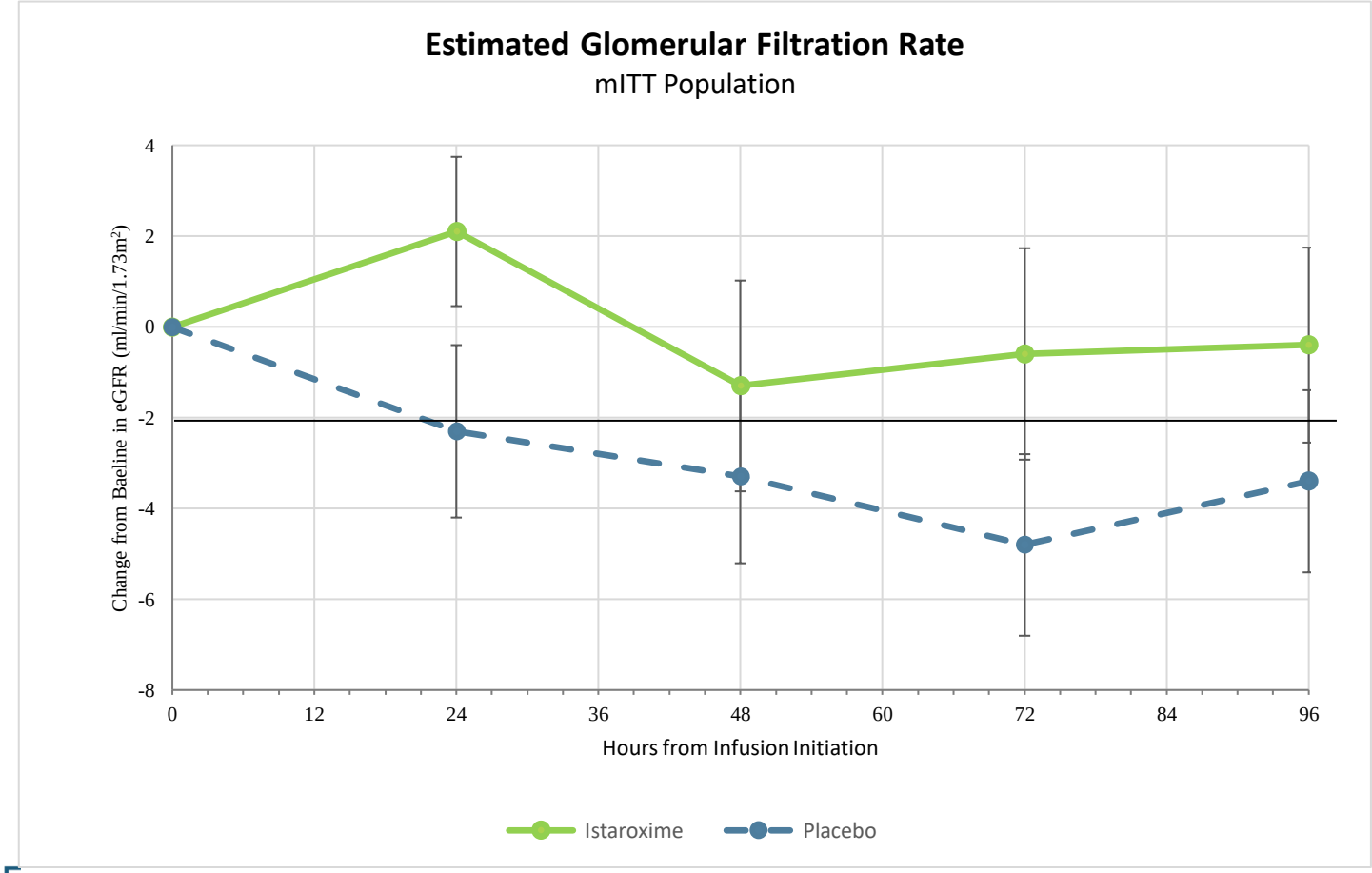
Cardiac Function Improvement

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

- Cardiac index significantly increased
- Stroke volume substantially increased and approached statistical significance
- Other echocardiographic measurements significantly 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 Positive Renal Profile

- Renal function was not decreased with istaroxime infusion
- Istaroxime treated patients also had greater diuresis with less cumulative diuretic use



Data shown as means and standard errors

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Serious Adverse Events and Adverse Drug Reactions

Event	Istaroxime (N=29)	Placebo (N=31)
All adverse events	27 (93%)	25 (81%)
Serious adverse events	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
Adverse drug reactions†	15 (52%)	3 (10%)
Gastrointestinal‡	9 (31%)	2 (6%)
Infusion site pain/inflammation	4 (14%)	1 (3%)

Note: data shown as n (%); patients can have more than one event during the 30-day follow up period
† Adverse drug reactions are AEs possibly related or related to study drug
‡ Most common - nausea, vomiting

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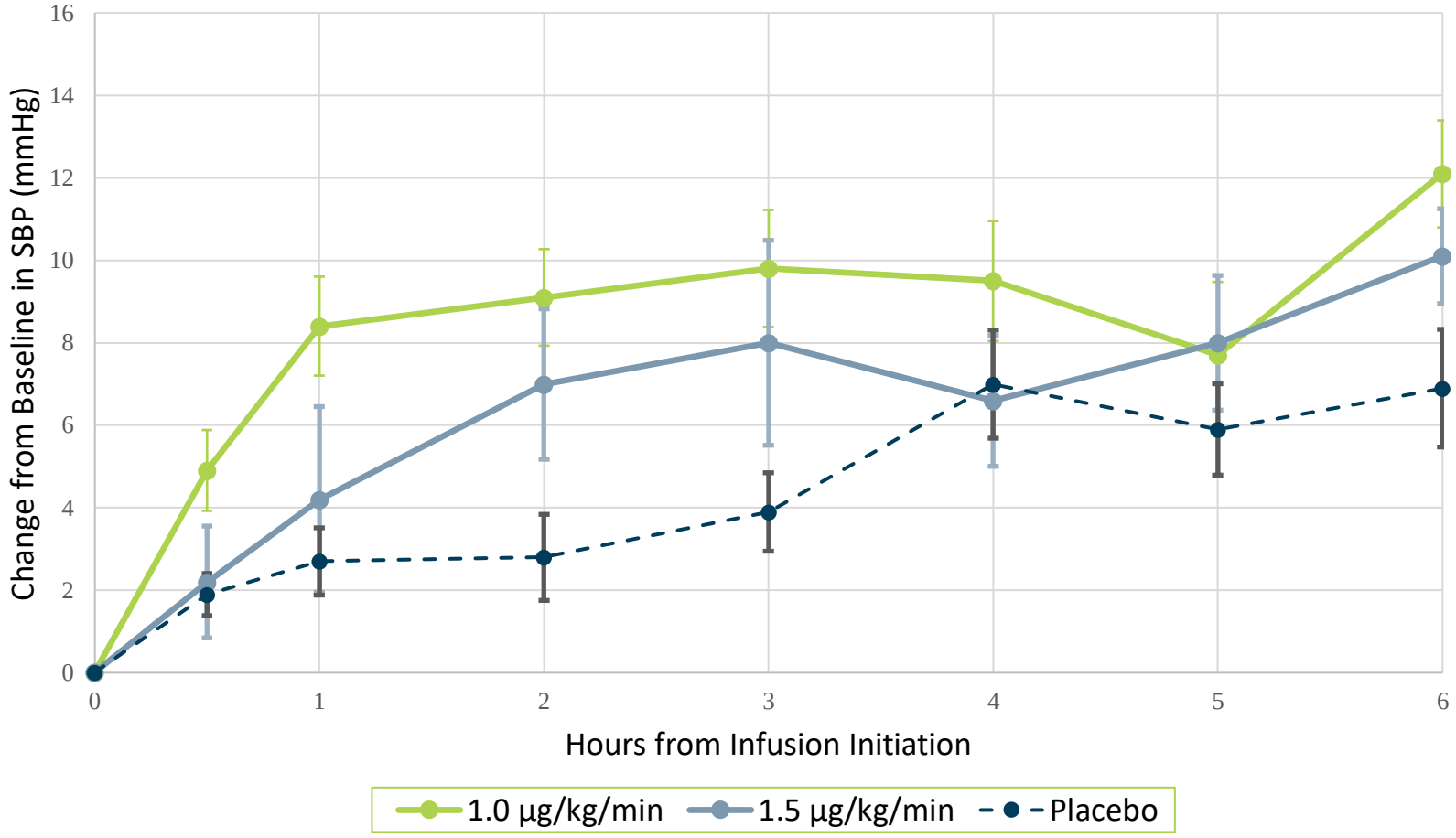
Comparison of Doses

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



All Subjects (n=60)

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:

- Attractive 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%)

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* LS-Means and associated p-values from ANCOVA model adjusted for pooled site, treatment, and baseline systolic BP.

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 and istaroxime treated patients tended to experience greater diuresis than placebo
- SEISMiC provided valuable information for optimizing our dose moving forward
- These data substantiate and advance the rationale for istaroxime as a treatment for AHF as well as enable us to continue to progress the program in cardiogenic shock

SEISMiC Trial –
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 agents)

Cardiogenic Shock Development Strategy

SEISMiC Study

- Proof of Concept
- SCAI Stage B due to AHF
- Learnings about dosing and effect, etc.

SEISMiC Extension Study

- Optimize the dosing
- Additional characterization of effect

SCAI Stage C Study

- Gain experience in SCAI stage C patients

Phase 3*

- Execute EOP2 meeting with these 3 studies augmented by AHF safety data base, etc.
- Target Phase 3 start in 2023

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** Progression to Phase 3 dependent upon trial results, regulatory alignment and resourcing*

SEISMiC Extension Study (amendment to the ECS 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

Study 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

1) 1.0 µg/kg/min for 24 hours, titrated down to 0.5 µg/kg/min for 24 hours, titrated to 0.25 µg/kg/min for 12 hours or
2) 1.0 µg/kg/min for 12 hours, titrated to 0.5 µg/kg/min for 36 hours, or
3) Placebo control

Multiple physiologic measures associated with cardiac function, blood pressure and safety

Planned SCAI Stage C Cardiogenic Shock Patient Study

While a smaller group than SCAI stage B, given positive results in early cardiogenic shock, the strategy is to gain experience in more severe, SCAI stage C patients to support both regulatory, development and commercial strategies

Study objectives:

- ✓ Gain experience in SCAI Stage C patients
- ✓ Support regulatory and clinical strategy

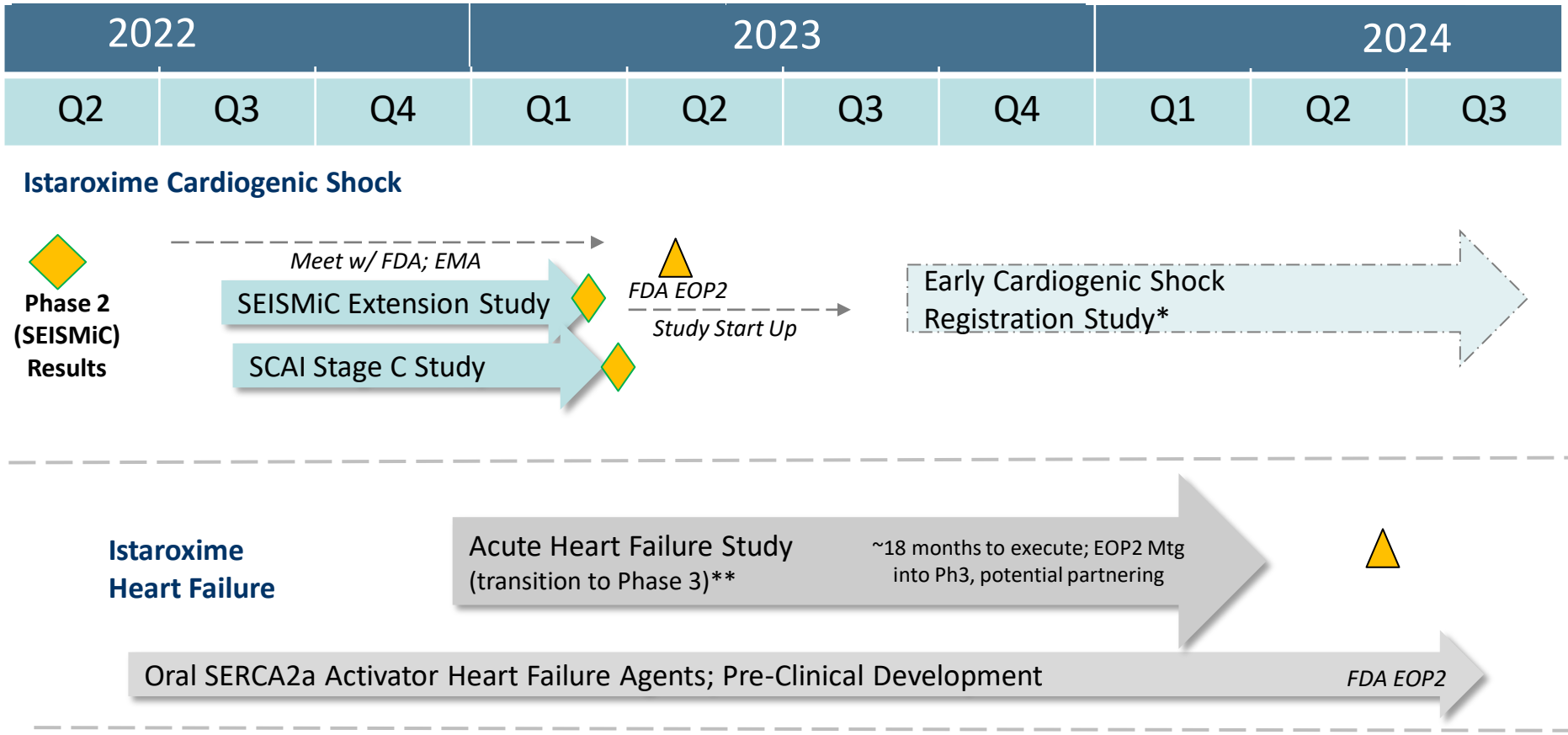
Study design:

Initial study in ~15-20 patients in the US with very low SBP and identified hypoperfusion that requires inotropic support.

Istaroxime infusions at 1.0 µg/kg/min, then titrated down
Non-responders can move to an approved inotrope, vasopressors

Blood pressure profile
Need for rescue medicine and devices / procedures
Safety and tolerability

Strategy for Value Creation



*study initiation pending positive data, regulatory input and adequate funding
**study initiation pending adequate funding

Summary -
Potential to Create Value

- Istaroxime has been successfully studied in 7 clinical trials (3 being Phase 2 trials) with approximately 300 patients treated with istaroxime to date (and plans to grow)
- Istaroxime has positive Phase 2a and 2b results demonstrating:
  - ✓ Improved cardiac function – without coming at the expense of….
  - ✓ Uniquely improved SBP and renal function
  - ✓ Favorable safety tolerability profile compared to existing therapies
- Early Cardiogenic Shock has significant unmet need and the positive results in our Phase 2 trial has created a valuable, additional program and option for the company. Pathway to approval and launch is expected to be both faster and cost less with a scale fitting of Windtree with an indication that is complimentary to AHF
- The AHF program will proceed with the sourcing of additional resources and/or non-dilutive support afforded by business development (which remains the ultimate, pre-phase 3 strategy for Istaroxime) while also advancing the next generation, oral SERCA2a activators for chronic and acute HF including HFpEF

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Q & A