UNITED STATES
SECURITIES AND EXCHANGE COMMISSION

Washington, DC 20549

FORM 8-K

CURRENT REPORT
Pursuant to Section 13 or 15(d)
of the Securities Exchange Act of 1934

Date of Report (Date of earliest event reported): June 14, 2023

Windtree Therapeutics, Inc.

(Exact name of registrant as specified in its charter)

Delaware	**001-39290**	**94-3171943**
(State or other jurisdiction of incorporation or organization)	**(Commission File Number)**	**(I.R.S. Employer Identification No.)**

2600 Kelly Road, Suite 100, Warrington, Pennsylvania	**18976**
(Address of principal executive offices)	**(Zip Code)**

Registrant's telephone number, including area code: (215) 488-9300

Not Applicable
(Former name or former address, if changed since last report)

Check the appropriate box below if the Form 8-K filing is intended to simultaneously satisfy the filing obligation of the registrant under any of the following provisions (see General Instruction A.2. below):

☐ Written communications pursuant to Rule 425 under the Securities Act (17 CFR 230.425)
☐ Soliciting material pursuant to Rule 14a-12 under the Exchange Act (17 CFR 240.14a-12)
☐ Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act (17 CFR 240.14d-2(b))
☐ Pre-commencement communications pursuant to Rule 13e-4(c) under the Exchange Act (17 CFR 240.13e-4(c))

Securities registered pursuant to Section 12(b) of the Act:

Title of each class	**Trading Symbol(s)**	**Name of each exchange on which registered**
Common Stock, par value $0.001 per share	WINT	The Nasdaq Capital Market

Indicate by check mark whether the registrant is an emerging growth company as defined in Rule 405 of the Securities Act of 1933 (§230.405 of this chapter) or Rule 12b-2 of the Securities Exchange Act of 1934 (§240.12b-2 of this chapter).

Emerging growth company ☐

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act. ☐

Item 8.01 Other Events.

On June 14, 2023, Windtree Therapeutics, Inc. (the "Company") updated information reflected in a slide presentation, which is filed herewith as Exhibit 99.1 to this Current Report on Form 8-K and is incorporated herein by reference. Representatives of the Company will use the updated presentation in various meetings with investors from time to time.

Item 9.01 Financial Statements and Exhibits.

(d) Exhibits

The following exhibits are being filed herewith:

Exhibit No.	Document
99.1	Corporate Presentation of Windtree Therapeutics, Inc.
104	Cover Page Interactive Data File (embedded within the Inline XBRL document).

SIGNATURES

Pursuant to the requirements of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned, thereunto duly authorized.

Dated: June 14, 2023

Windtree Therapeutics, Inc.
By: /s/ Craig E. Fraser
Name: *Craig E. Fraser*
Title: *President and Chief Executive Officer*

Exhibit 99.1


Windtree Therapeutics
R&D and Investor Day
June 14, 2023
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 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.

Welcome

Craig Fraser, President & CEO

Steve Simonson, MD

John Teerlink, MD

Agenda

- Introduce Windtree
- Overview the Cardiogenic Shock Market and Landscape
- Introduce Istaroxime and the Rationale for a Cardiogenic Shock Program
- SEISMiC Trial and Results
- Development Strategy and Plans to Transition to EOP2 / Phase 3
- Clinical Prospective on Need, Istaroxime Profile and Data
- Acute Heart Failure, Next Generation Compounds
- Business Development
- Short / Mid Focus for Value Creation, Cap and Cash
- Q&A

WINDTREE THERAPEUTICS

WINDTREE THERAPEUTICS™

- **Biopharmaceutical company with advanced clinical focus 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**
  - An acute heart failure and cardiogenic shock drug candidate that has demonstrated both significant improvement in cardiac function as well as rapid and significant improvement in blood pressure, with favorable effect on myocardial oxygen demand and renal function and 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**
- **Highly engaged in business development activities - including exploring strategic opportunities**
- **Lean, capital efficient operation led by a highly experienced management team**

Pipeline

Lead Products	Indication	Phase	Development Status	Regulatory Status
Istaroxime	Cardiogenic Shock	Phase 2	• Positive Phase 2 study • Planning the execution of the next study and plans to meet with regulatory agencies regarding development path	*Executed Phase 2 in early cardiogenic shock,*
Istaroxime	Acute Heart Failure	Phase 2b	• Augment AHF data with the efficacy, safety and dosing 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 with partnership	*FDA Fast Track Designation*
Oral SERCA2a Activators	Chronic Heart Failure, including potentially HFpEF	Preclinical	• Chronic and Acute Heart Failure • Target for collaboration/partnership	*IND-enabling studies*
Rostafuroxin	Treatment Resistant Hypertension - Genetically Associated	Phase 2b	• Phase 2 data in hypertension and genetically associated hypertension • Company repositioned for the attractive and large Resistant Hypertension market • Out-licensing opportunity	*Ex-U.S. filings Open U.S. IND*
KL4 Surfactant and AEROSURF	KL4 surfactant Drug/Device Tx for RDS and potential other applications	Phase 2b	• Global out-license to Lee's Pharmaceuticals	*FDA Fast Track Designation, Orphan Drug*

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Istaroxime

Cardiogenic Shock

Potential indication in active clinical development

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Cardiogenic Shock

A severe presentation of heart failure characterized by **very low blood pressure and flow to and from the body and vital organs (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[1]
- Represents an approximate $1.25B total market potential[2]

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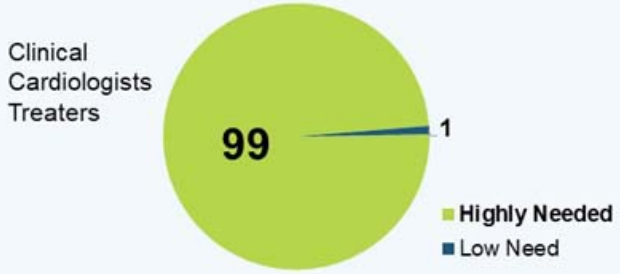
1) Kolte D, American Heart Association; 2014 Jan 13; 2) Estimates from claims data and epi data September 2021, multiplied by assumed various regional prices

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

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

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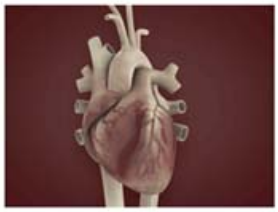
Market research conducted by Sermo, a leading provider of real time physician insights

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** and subsequent contraction cycle via stimulation of SERCA2a activity which enhances calcium reuptake

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

May also increase BP via a direct effect on vascular smooth muscle

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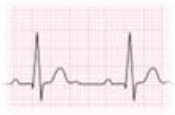
Rationale for Istaroxime in Cardiogenic Shock Came from AHF Phase 2 Trials

Cardiac Function Improved

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

Dose-related Increase in Systolic Blood Pressure

Maintain or Increase Renal Function (eGFR)



Dose-related Decreases in Heart Rate

No increase in clinically significant arrythmias

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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 75-90mmHg) 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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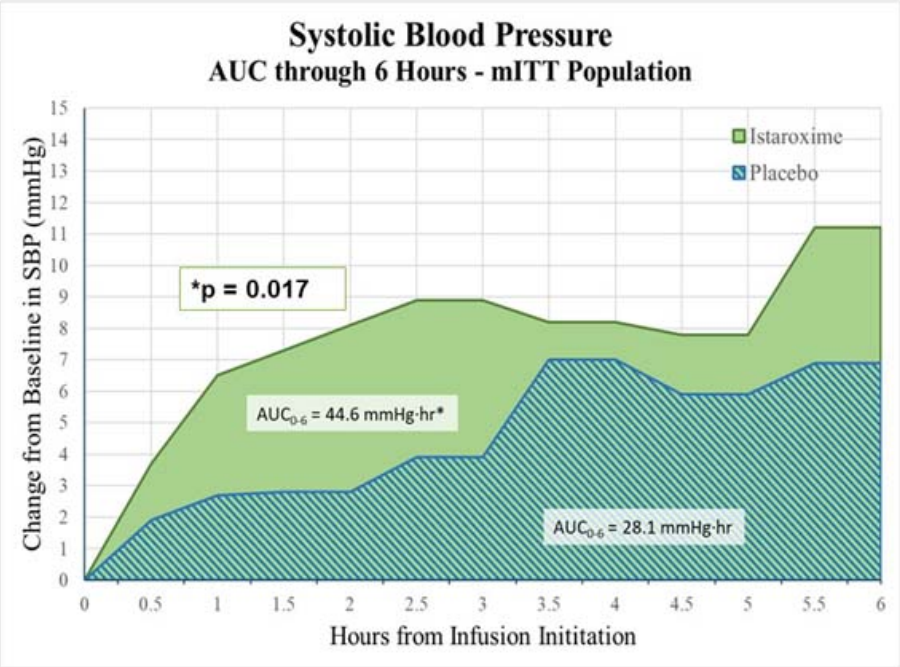
Difference in SBP Profile



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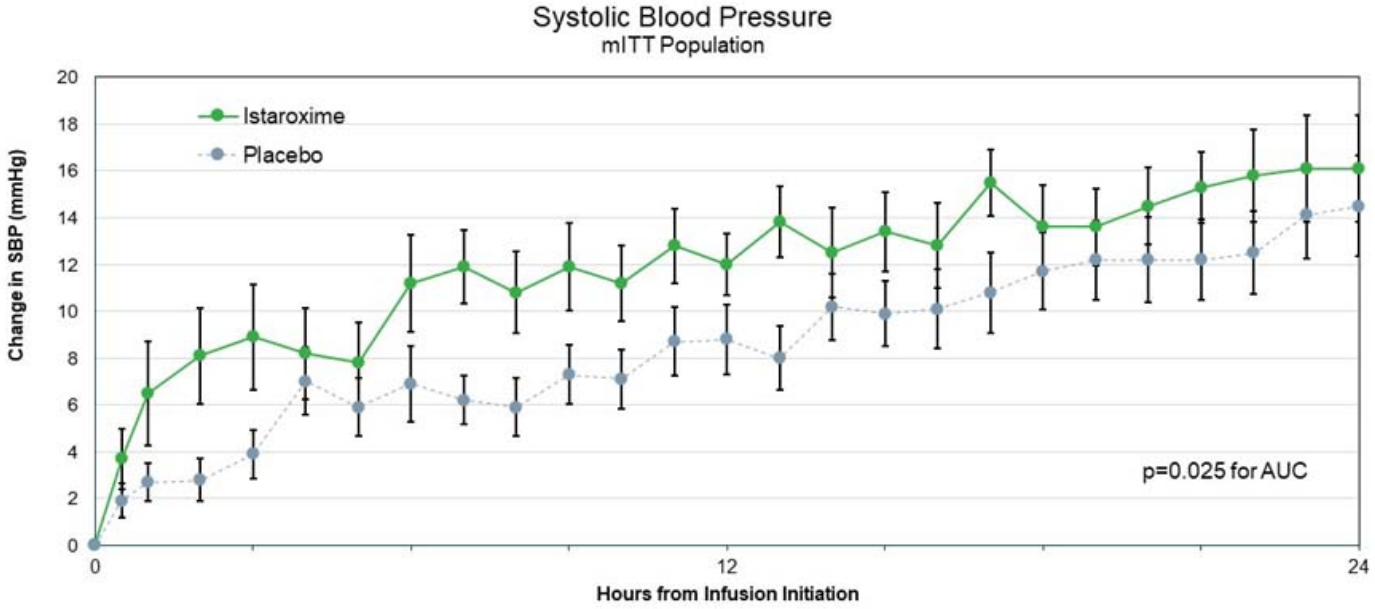
Systolic BP Improvements Persisted over 24 Hours



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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**
  - (4 mL/m^2) approaching statistical significance
- ✓**Other parameters were also 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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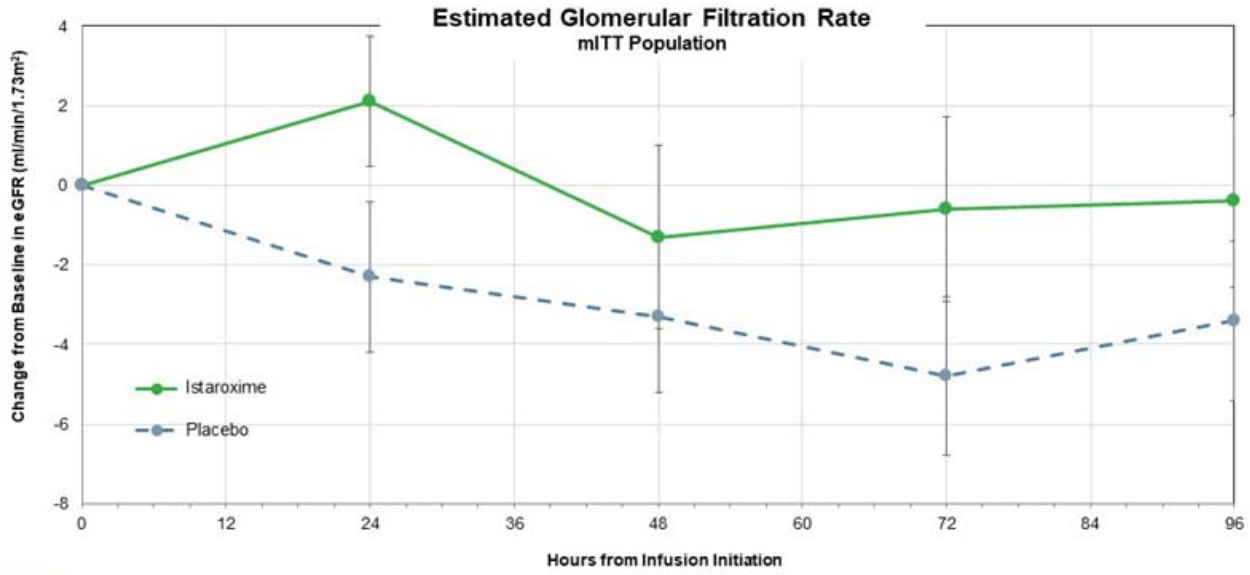
Treatment was Associated with a Favorable Renal Profile

Renal function was not decreased in istaroxime treated patients



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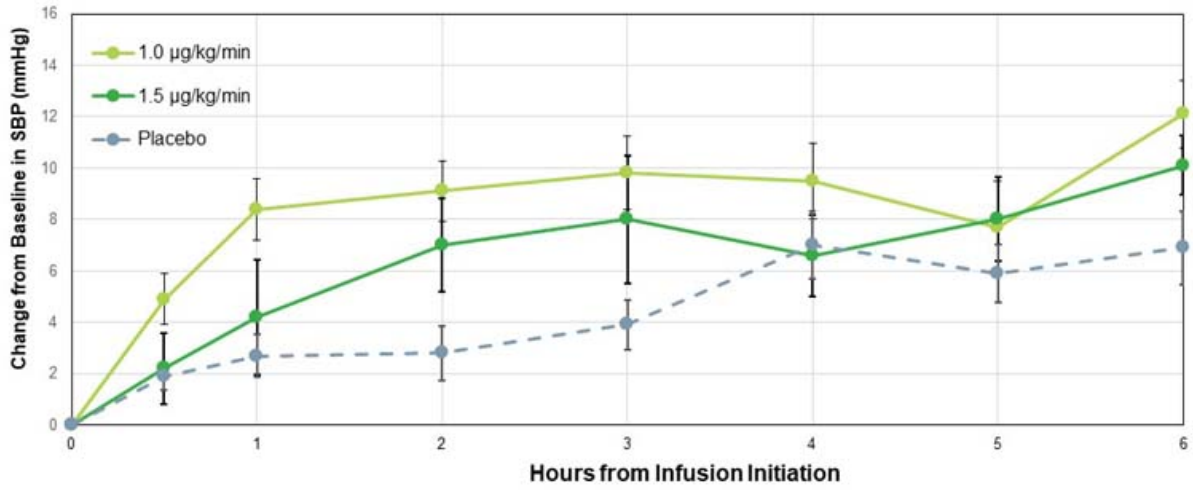
Data shown as means and standard errors

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



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All Subjects (n=60)

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

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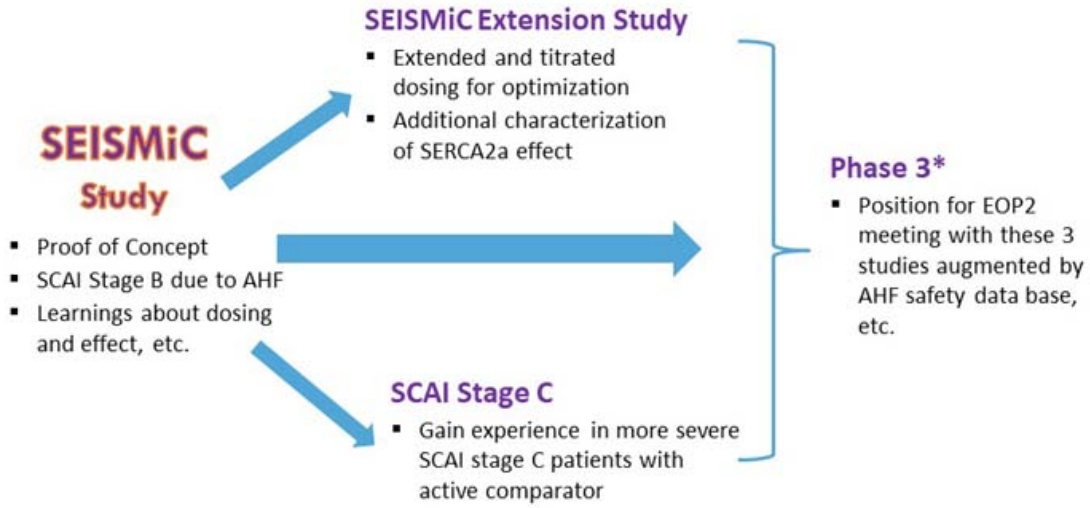
Cardiogenic Shock Development Strategy



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** 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 with SBP between 70-100mmHg conducted in sites in the US, EU and LATAM

Two istaroxime doses versus placebo.
Istaroxime dosed for up to 60-hours, decreasing the dose over time

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

~8 months to execute enrollment and $3.8MM
Study plans and progression dependent upon regulatory alignment and capital resourcing

Descriptors of SCAI Shock Stages:

Stage	Description	Physical exam/bedside findings	Biochemical markers	Hemodynamics
A At risk	A patient who is not currently experiencing signs or symptoms of CS, but is at risk for its development. These patients may include those with large acute myocardial infarction or prior infarction acute and/or acute on chronic heart failure symptoms.	Normal JVP Lung sounds clear Warm and well perfused • Strong distal pulses • Normal mentation	Normal labs • Normal renal function • Normal lactic acid	Normotensive (SBP≥100 or normal for pt.) If hemodynamics done • cardiac index ≥2.5 • CVP <10 • PA sat ≥65%
B Beginning CS	A patient who has clinical evidence of relative hypotension or tachycardia without hypoperfusion.	Elevated JVP Rales in lung fields Warm and well perfused • Strong distal pulses • Normal mentation	Normal lactate Minimal renal function impairment Elevated BNP	SBP <90 **OR** MAP <60 **OR** >30 mmHg drop from baseline Pulse ≥100 If hemodynamics done • cardiac index ≥2.2 • PA sat ≥65%
C Classic CS	A patient that manifests with hypoperfusion that requires intervention (inotrope, pressor or mechanical support, including ECMO) beyond volume resuscitation to restore perfusion. These patients typically present with relative hypotension.	***May Include Any of:*** Looks unwell Panicked Ashen, mottled, dusky Volume overload Extensive rales Killip class 3 or 4 BiPap or mechanical ventilation Cold, clammy Acute alteration in mental status Urine output <30 mL/h	***May Include Any of:*** Lactate ≥2 Creatinine doubling **OR** >50% drop in GFR Increased LFTs Elevated BNP	***May Include Any of:*** SBP <90 **OR** MAP <60 **OR** >30 mmHg drop from baseline **AND** drugs/device used to maintain BP above these targets Hemodynamics • cardiac index <2.2 • PCWP >15 • RAP/PCWP ≥0.8 • PAPI <1.85 • cardiac power output ≤0.6
D Deteriorating/ doom	A patient that is similar to category C but are getting worse. They have failure to respond to initial interventions.	***Any of stage C***	***Any of Stage C AND:*** Deteriorating	***Any of Stage C AND:*** Requiring multiple pressors **OR** addition of mechanical circulatory support devices to maintain perfusion
E Extremis	A patient that is experiencing cardiac arrest with ongoing CPR and/or ECMO, being supported by multiple interventions.	Near Pulselessness Cardiac collapse Mechanical ventilation Defibrillator used	"Trying to die" CPR (A-modifier) pH ≤7.2 Lactate ≥5	No SBP without resuscitation PEA or refractory VT/VF Hypotension despite maximal support

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SCAI Stage C Study

Study Objectives:

- 20 patients with SCAI Stage C shock due to ADHF: Hypotension + hypoperfusion
  Protocol will allow additional enrollment after this review

- Istaroxime or placebo will be added to initial standard of care shock therapy (blinded)
- Hold shock therapies constant for 6 hours to assess the primary BP endpoint, changes are allowed if the patient's condition dictates

- Thereafter, taper the initial shock therapy with istaroxime supporting the patient
- Key Measurements include:
  - SBP over 6 hours

  - Vasopressor score
  - Clinically significant arrhythmias
  - Renal function
  - Progression to greater shock stage

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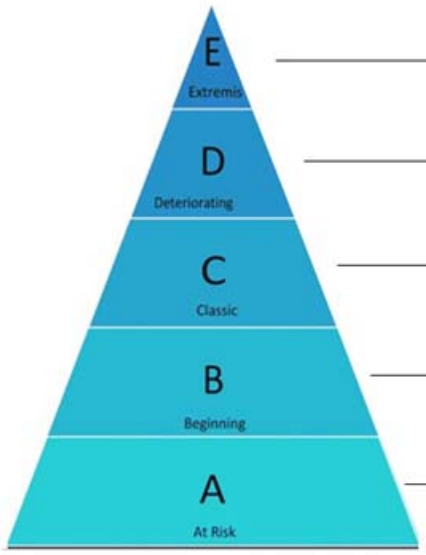
Our Development Plan (studying SCAI stage B, C) Designed To Maximize Cardiogenic Shock Addressable Market



% of CS Patients, Experiencing Early to Extreme CS

- E Extremis → 2%
- D Deteriorating → 12%

Very severe and unstable:
– mechanical intervention

- C Classic → 30%
- B Beginning → 56%

B+C: 86%

SCAI B, C: Focus for Ista CS Development

- SCAI C characterized by organ / tissue hypoperfusion

- A At Risk →

"A- At Risk" patients will likely be covered in Ph3 AHF trial

- ie. low SBP ~115-90mmHg, etc.

https://www.uscjournal.com/articles/describing-and-classifying-shock-recent-insights

SCAI stage A are removed from the calculation

Blood pressure by SCAI stage is shown on slide 20

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Cardiogenic Shock Opportunity

Average length of stay in U.S. ~19.5 days: >$200k in patient costs

OPPORTUNITY DRIVERS

- ✓ Currently available pharmacologic treatments have undesirable side effects and poor outcomes
- ✓ Very high cost of cardiogenic shock treatment creates opportunity for istaroxime pharmacoeconomic benefits
- ✓ Lack of active competition in development or the market
- ✓ Attractive commercial market potential (as well as time and cost of development)

INTENDED POSITIONING:

1. **Expand the Market due to Profile:** SCAI Stage B / Early Cardiogenic Shock (where vasopressors are reserved) to help stabilize the patient and prevent deterioration
2. **Become the Preferred Agent:** Preferred agent with first line use in SCAI Stage C / Classic Cardiogenic Shock

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

John R. Teerlink, MD

- Harvard Medical School followed by an internal medicine residency at the University of California San Francisco (UCSF). He continued a post-doctoral research fellowship at Hoffman-LaRoche in Basel, Switzerland. Dr. Teerlink completed his cardiovascular medicine fellowship and a Howard Hughes post-doctoral research fellowship at UCSF, subsequently joining the faculty, where he currently is a Professor of Clinical Medicine.
- Director of Heart Failure and of the Echocardiography Laboratory, San Francisco Veterans Affairs Medical Center
- Active leader in US and European Heart Failure medical associations.
- Dr. Teerlink has been the principal investigator in many of the largest heart failure and cardiogenic shock studies and recently served a four-year term on the FDA's Cardiovascular and Renal Advisory Committee.

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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

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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

Objective: Evaluate potential Phase 3 AHF program based on data from our cardiogenic shock program

Potential Phase 3 AHF Program

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 early 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.

We currently seek partnership to execute this clinical trial

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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+/K+) 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

Active Engagement in Out-License and Partnership Opportunities

Global / Regional Licensing

- ✓ **AEROSURF / KL4 Platform** – Exclusive global license to Lee's Pharm (SEHK:950) and Zhaoke. Potential proceeds:
  - Up to $78.9 million in potential milestone payments
  - Low double-digit % royalties
  - *WINT no longer carries any costs for KL4 platform*

Potential licensing opportunities

- **Istaroxime – AHF and Cardiogenic Shock**
- **SERCA2a Activators – Chronic and Acute Heart Failure**
- **Rostafuroxin – Treatment Resistant Hypertension**

Strategic Transaction

Mergers & Acquisitions

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Strategy for Value-Creation -
Focus for the Next 4-6 Quarters

Clinical Milestones
- Strong trial execution of Extension and Stage C
- Enable transition to EOP2/Ph3
- Execute select CMC actions

Transformative BD
- Licensing and partnership for non-dilutive value
- Strategic: Increase value, portfolio with enhanced opportunities and mitigated risk

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WINT Team

Retention, Motivation and Performance Culture

High IR/PR Communication
- Deliverables and news, dedicated media, etc.

Financial Summary & Capitalization

Cash

March 31, 2023	**$4.2M**
March 31, 2023 Pro Forma	**$15.0M**

Securities	**Common Equivalents** as of April 30, 2023
Common Stock	5,147,919
Options (WAEP $376.68)	70,972
RSUs	6,524
Warrants (WAEP $19.90)	4,688,251
Fully Diluted	9,913,666

Driving Capital Efficiency to Program Investment

Significantly reduced company expenses and cash burn via out-licensing KL4 platform, focused resources on lead priority program

- **58%** Total Company Burn / Month Reduction Q1'22 vs. Q1'23
- **53%** Non-Program Burn / Month Reduction Q1'22 vs. Q1'23
- **46%** FTE Reduction Q1'22 vs. Q1'23

While the Company has plans to start new studies, it plans to also continue to lower non-program cash burn moving forward

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Q&A

www.Windtreetx.com

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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**

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1) ADHERE Registry, n=48,567; JAMA 2006
2) European Journal of Heart Failure; Voors, PRE-RELAX AHF Study; 2011; 13

Cardiogenic Shock Treatment
Istaroxime Potential Opportunity for Regulatory Pathway

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

FDA Regulatory Pathway Assumptions

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]

End of Phase 2 meeting will confirm requirements for Phase 3:

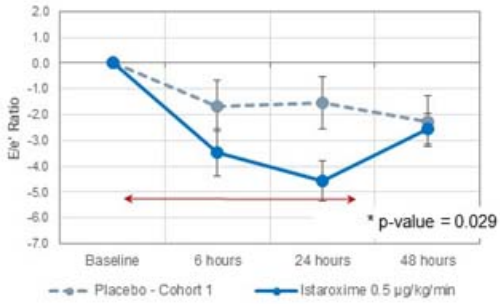
- Endpoint is blood pressure increase
- Superior mortality over control group endpoint is not required
- Smaller number of subjects required than typical cardiovascular clinical trials

WINDTREE THERAPEUTICS

1) Kosaraju A, Hai O. Cardiogenic Shock. [Updated 2019 Jan 25]. In: www.ncbi.nlm.nih.gov/books/NBK482255/ CSRC Think Tank - July 24, 2019

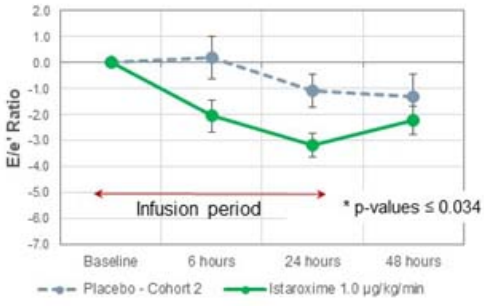
Primary Endpoint Achieved
Significant Changes in E/e' Ratio[1] and Stroke Volume

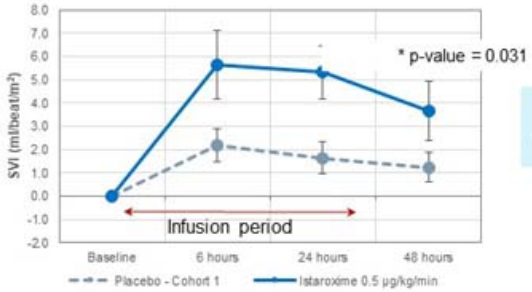
Istaroxime 0.5 µg/kg/min vs. placebo



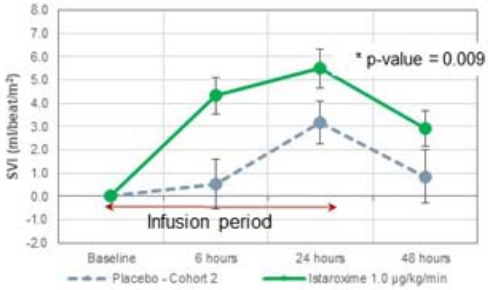
E/e'

Istaroxime 1.0 µg/kg/min vs. placebo





Stroke Volume

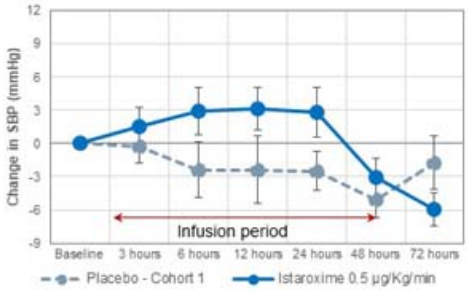


WINDTREE THERAPEUTICS

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

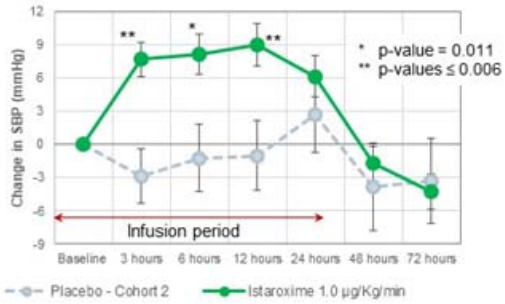
Systolic Blood Pressure Increased During Treatment and Renal Function Tended to Improve

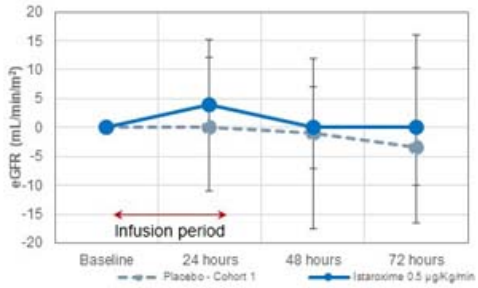
Istaroxime 0.5 µg/kg/min vs. placebo



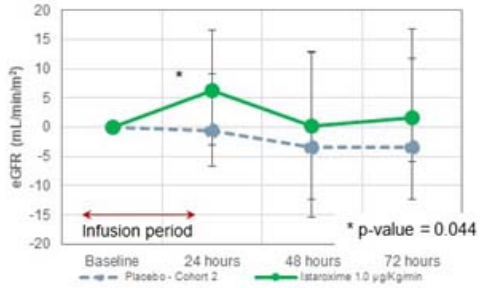
Systolic Blood Pressure (SBP)

Istaroxime 1.0 µg/kg/min vs. placebo





GFR (Renal Function)

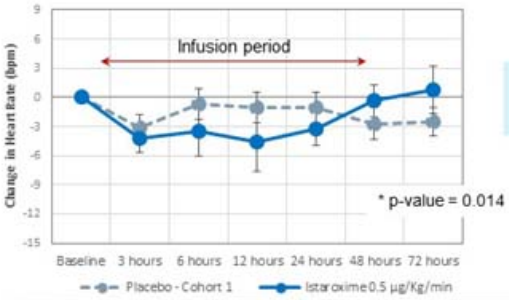


WINDTREE THERAPEUTICS

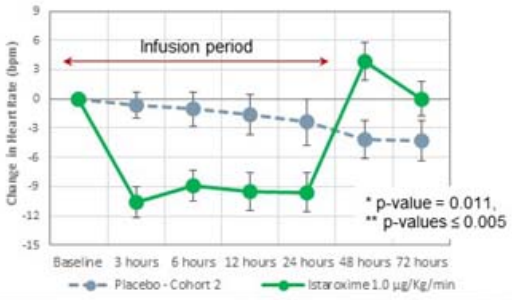
Data shown as means and standard errors

Heart Rate Decreased and No Increases in Cardiac Troponins

Istaroxime 0.5 µg/kg/min vs. placebo

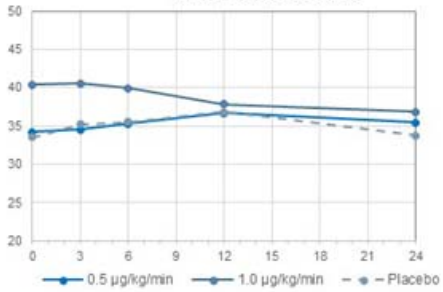


Istaroxime 1.0 µg/kg/min vs. placebo

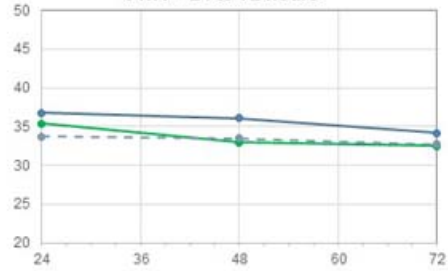


Heart Rate

cTnT – 0 to 24 hours



cTnT – 24 to 72 hours



Cardiac TnT (Myocardial Damage)

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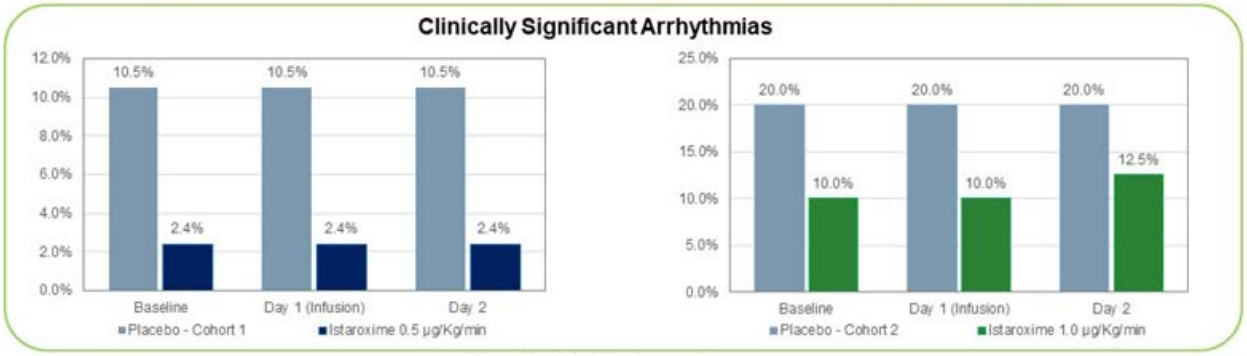
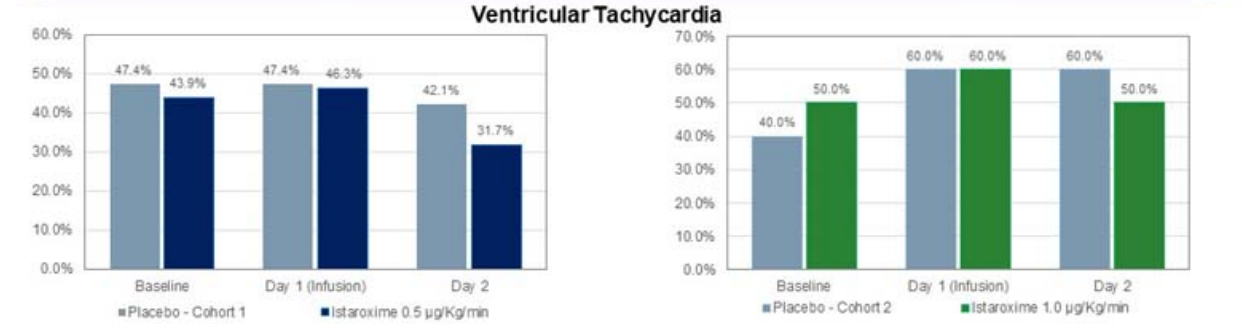
Favorable Profile Observed with 24-hour Holter Monitoring





WINDTREE THERAPEUTICS

PVCs (n*/24 hours) shown as median, ventricular tachycardia and clinically significant arrhythmias shown as percentage of patients

Adverse Events

Event	Pooled placebo (n=39)	Istaroxime 0.5 mg/Kg/min (n=41)	Istaroxime 1.0 mg/Kg/min (n=40)
All adverse events	23 (59.0%)	31 (75.6%)	33 (82.5%)
Adverse events leading to discontinuation	1 (2.6%)	-	4 (10.0%)
Serious adverse events	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%)	-	-
Adverse Drug Reactions†	10 (25.6%)	23 (56.1%)	25 (62.5%)
Cardiovascular††	**9 (23.1%)**	**4 (9.8%)**	**7 (17.5%)**
Gastrointestinal‡	2 (5.1%)	4 (9.8%)	14 (38.0%)
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

WINDTREE THERAPEUTICS

From CVT-CV-002 (2b)

Rostafuroxin – A Potential New Treatment for Resistant Hypertension (RHTN)

Rostafuroxin

Specifically displaces ouabain binding from the high affinity Na+–K+ATPase isoform present in the caveolae, antagonizing all the functional effects of ouabain

Studies have reported a correlation of ouabain and aldosterone* (the target of the Cincor and Mineralys Phase 2 studies) in patients with RHTN

There have been seven clinical studies of rostafuroxin in treatment naïve hypertension (patients without any treatment), including 4 Phase 2 studies which examined the antihypertensive effect, safety and tolerability

*Rossi G, Manunta P, Hamlyn JM, et al. Immunoreactive endogenous ouabain primary aldosteronism and essential hypertension: relationship with plasma renin, aldosterone and blood pressure levels. *J Hypertens* 1995;13(10):1181.

*Borio G, Tentori S, Faroffi F, et al. Endogenous ouabain and aldosterone are coelevated in the circulation of patients with essential hypertension. *Intern Emerg Med* 2022;1.

*Manunta P, Hamlyn JM, Simonini M, et al. Endogenous ouabain and the renin-angiotensin-aldosterone system: distinct effects on Na handling and blood pressure in human hypertension. *J Hypertens* 2011;29(2):349.

High Potential Value in Treatment Resistant Hypertension Market

Large Market with Significant Unmet Need

- Treatment resistant hypertension
  - An estimated 10% to 20% of hypertensive patients have resistant hypertension, defined as having controlled or uncontrolled blood pressure with the use of ≥ 3 medications that includes a diuretic*
- Effective hypertension treatment is critical to reducing cardiovascular and renal disease; yet millions of hypertensive patients in the United States are not at goal despite treatment

Significant Value Potential

- Two biotech companies have demonstrated the significant value the market is placing on RHTN with Phase 2 results
- Cincor acquisition by AstraZeneca (Jan 9, 2023)
  - Total consideration would be approximately $1.8 billion (a 206% premium over CinCor's closing market price on January 6, 2023)
- Mineralys executes IPO and raises $192MM (Feb 13, 2023)

WINDTREE THERAPEUTICS

*Carey RM, Sakhuja S, Calhoun DA, Whelton PK, Muntner P. Prevalence of Apparent Treatment-Resistant Hypertension in the United States. *Hypertension* 2019;73:424.; AHA. High Blood Pressure Among Black People, <https://www.heart.org/en/health-topics/high-bloodpressure/why-high-blood-pressure-is-a-silent-killer/high-blood-pressure-and-african-americans> (2022).; *Roberie DR, Elliott WJ. What is the prevalence of resistant hypertension in the United States? *Curr Opin Cardiol* 2012;27(4):385.; *Sim JJ, Bhandari SK, Shi J, et al. Characteristics of resistant hypertension in a large, ethnically diverse hypertension population of an integrated health system. *Mayo Clin Proc* 2013 ;88(10):1099 *Calhoun DA, Jones D, Textor S, et al. Resistant hypertension: diagnosis, evaluation, and treatment: a scientific statement from the American Heart Association Professional Education Committee of the Council for High Blood Pressure Research. *Circulation* 2008;117(25):e510-526