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): March 15, 2022

Windtree Therapeutics, Inc.

(Exact name of registrant as specified in its charter)

Delaware	**000-26422**	**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 March 15, 2022, Windtree Therapeutics, Inc. (the "***Company***") issued a press release announcing the completion of enrollment in its phase 2 study of istaroxime in early cardiogenic shock caused by heart failure. A copy of the press release is attached as Exhibit 99.1 to this Current Report on Form 8-K and is incorporated herein by reference.

In addition, on March 15, 2022, the Company updated information reflected in a slide presentation, which is attached as Exhibit 99.2 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	Press Release of Windtree Therapeutics, Inc., dated March 15, 2022, announcing the completion of enrollment in its phase 2 study of istaroxime in early cardiogenic shock caused by heart failure.
99.2	Investor 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.

Windtree Therapeutics, Inc.

By: /s/ Craig Fraser
Name: Craig Fraser
Title: President and Chief Executive Officer

Date: March 15, 2022

Exhibit 99.1

Windtree Completes Enrollment of Phase 2 Study of Istaroxime in Early Cardiogenic Shock

On track for top-line data in April 2022

WARRINGTON, PA – **March 15, 2022** – Windtree Therapeutics, Inc. (NasdaqCM: WINT), a biotechnology company focused on advancing multiple late-stage interventions for acute cardiovascular and pulmonary disorders, today announced it has successfully completed enrollment in its phase 2 study of istaroxime in early cardiogenic shock caused by heart failure.

The study is an international, randomized double-blind, placebo-controlled study designed to assess the efficacy and safety of istaroxime and to support an intended pathway for the development in early cardiogenic shock. The study has enrolled 60 Society for Cardiovascular Angiography & Interventions (SCAI) class B early cardiogenic shock patients with severe heart failure (30 assigned to istaroxime and 30 assigned to placebo) and systolic blood pressures (SBP) between 75-90 mmHg. Study drug was administered over 24 hours. The primary endpoint is the SBP profile over the first 6 hours after initiating the infusion. Secondary endpoints will include various assessments of blood pressure changes over 24 hours and measures associated with safety and tolerability. All patients will complete a 30-day follow-up prior to database lock and generation of topline data; as a result, topline data is expected to be announced in April.

“We are very pleased to have completed enrollment in the study of istaroxime in early cardiogenic shock due to heart failure. We are eager to examine the potential of istaroxime in this critical condition. The efforts of participating centers to enroll patients are much appreciated given the challenges of conducting research in hospital cardiac care units during the global pandemic,” said Steve Simonson, MD, CMO of Windtree Therapeutics.

Cardiogenic shock is a serious condition that occurs when the heart is failing significantly and cannot pump enough blood and oxygen to the brain, kidneys, and other vital organs. Mortality rates are significant and, depending on severity, range from 7% to 40% in the U.S. There is a lack of satisfactory pharmacological intervention to reverse the condition as 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. Market research revealed 99% of 100 U.S.-based clinical cardiologists interviewed who treat cardiogenic shock patients responded that new drug innovation to treat SCAI class B cardiogenic shock patients is highly needed. The cardiogenic shock worldwide total market value is estimated to be $1.25 billion.

Craig Fraser, CEO and President of Windtree Therapeutics added, “Early cardiogenic shock patients need new therapies that can be used earlier and more broadly to rapidly improve blood pressure and cardiac function without many of the unwanted side effects of existing, older agents that often cause cardiologists to reserve using them. We look forward to announcing topline data and our continued execution of this program, as well as the larger acute heart failure program, as we move forward in developing istaroxime as an innovative new therapy.”

About Istaroxime
Istaroxime is a first-in-class, dual mechanism therapy designed to improve both systolic and diastolic cardiac function. Istaroxime is a positive inotropic agent that increases myocardial contractility through inhibition of Na+/K+- ATPase with a complementary mechanism that facilitates myocardial relaxation through activation of the SERCA2a calcium pump on the sarcoplasmic reticulum, enhancing calcium reuptake from the cytoplasm. Data from two phase 2 studies in patients with acute heart failure (AHF) demonstrate that istaroxime infused intravenously significantly improves cardiac function and blood pressure without increasing heart rate or cardiac rhythm disturbances and was generally well tolerated.

About Windtree Therapeutics
Windtree Therapeutics, Inc. is advancing multiple late-stage interventions for acute cardiovascular and acute pulmonary disorders to treat patients in moments of crisis. Using new scientific and clinical approaches, Windtree is developing a multi-asset franchise anchored around compounds with an ability to activate SERCA2a, with lead candidate, istaroxime, being developed as a first-in-class treatment for acute heart failure and for early cardiogenic shock. Windtree's heart failure platform includes follow-on oral pre-clinical SERCA2a activator assets as well. In pulmonary care, Windtree has focused on facilitating the transfer of the clinical development of AEROSURF®, to its licensee in Asia, Lee's HK. Windtree is also evaluating KL4 surfactant for the treatment of acute respiratory distress syndrome in COVID-19 patients. Included in Windtree's portfolio is rostafuroxin, a novel precision drug product targeting hypertensive patients with certain genetic profiles.

Forward-Looking Statements
This press release contains forward-looking statements within the meaning of The Private Securities Litigation Reform Act of 1995. The Company may, in some cases, use terms such as "predicts," "believes," "potential," "proposed," "continue," "estimates," "anticipates," "expects," "plans," "intends," "may," "could," "might," "will," "should" or other words that convey uncertainty of future events or outcomes to identify these forward-looking statements. Such statements are based on information available to the Company as of the date of this press release and are subject to numerous important factors, risks and uncertainties that may cause actual events or results to differ materially from the Company's current expectations. Examples of such risks and uncertainties include: risks and uncertainties associated with the ongoing economic and social consequences of the COVID-19 pandemic, including any adverse impact on the Company's clinical trials, clinical trial timelines or disruption in supply chain; the success and advancement of the clinical development programs for istaroxime, KL4 surfactant and the Company's other product candidates; the impacts of political unrest, including as a result geopolitical tension, including escalation in the conflict between Russia and Ukraine and any additional resulting sanctions, export controls or other restrictive actions that may be imposed by the United States and/or other countries, which could have an adverse impact on the Company's clinical trials and clinical trial timelines, in particular with respect to clinical trial sites in Russia, or disruption in supply chain and disruption, instability and volatility in the global markets, which could have an adverse impact on the Company's ability to access the capital markets; the Company's ability to secure significant additional capital as and when needed; the Company's ability to access the debt or equity markets; the Company's ability to manage costs and execute on its operational and budget plans; the results, cost and timing of the Company's clinical development programs, including any delays to such clinical trials relating to enrollment or site initiation; risks related to technology transfers to contract manufacturers and manufacturing development activities; delays encountered by the Company, contract manufacturers or suppliers in manufacturing drug products, drug substances, aerosol delivery systems (ADS) and other materials on a timely basis and in sufficient amounts; risks relating to rigorous regulatory requirements, including that: (i) the FDA or other regulatory authorities may not agree with the Company on matters raised during regulatory reviews, may require significant additional activities, or may not accept or may withhold or delay consideration of applications, or may not approve or may limit approval of the Company's product candidates, and (ii) changes in the national or international political and regulatory environment may make it more difficult to gain regulatory approvals and risks related to the Company's efforts to maintain and protect the patents and licenses related to its product candidates; risks that the Company may never realize the value of its intangible assets and have to incur future impairment charges; risks related to the size and growth potential of the markets for the Company's product candidates, and the Company's ability to service those markets; the Company's ability to develop sales and marketing capabilities, whether alone or with potential future collaborators; and the rate and degree of market acceptance of the Company's product candidates, if approved. These and other risks are described in the Company's periodic reports, including the annual report on Form 10-K, quarterly reports on Form 10-Q and current reports on Form 8-K, filed with or furnished to the Securities and Exchange Commission and available at www.sec.gov. Any forward-looking statements that the Company makes in this press release speak only as of the date of this press release. The Company assumes no obligation to update forward-looking statements whether as a result of new information, future events or otherwise, after the date of this press release.

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Windtree Therapeutics

Company Overview

March 2022

(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 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.

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.

Windtree Therapeutics Highlights

- Biopharmaceutical company with **advanced clinical programs** spanning cardiovascular and respiratory disease states (NASDAQ: WINT)

- Clinical programs focused on **significant markets with high unmet needs and with supportive regulatory paths**:
  - One clinical program received both Fast Track and Orphan Drug designations; another clinical program received Fast Track designation with potential for Breakthrough designation

- **Several clinical and business milestones** planned which may have the potential to be growth catalysts

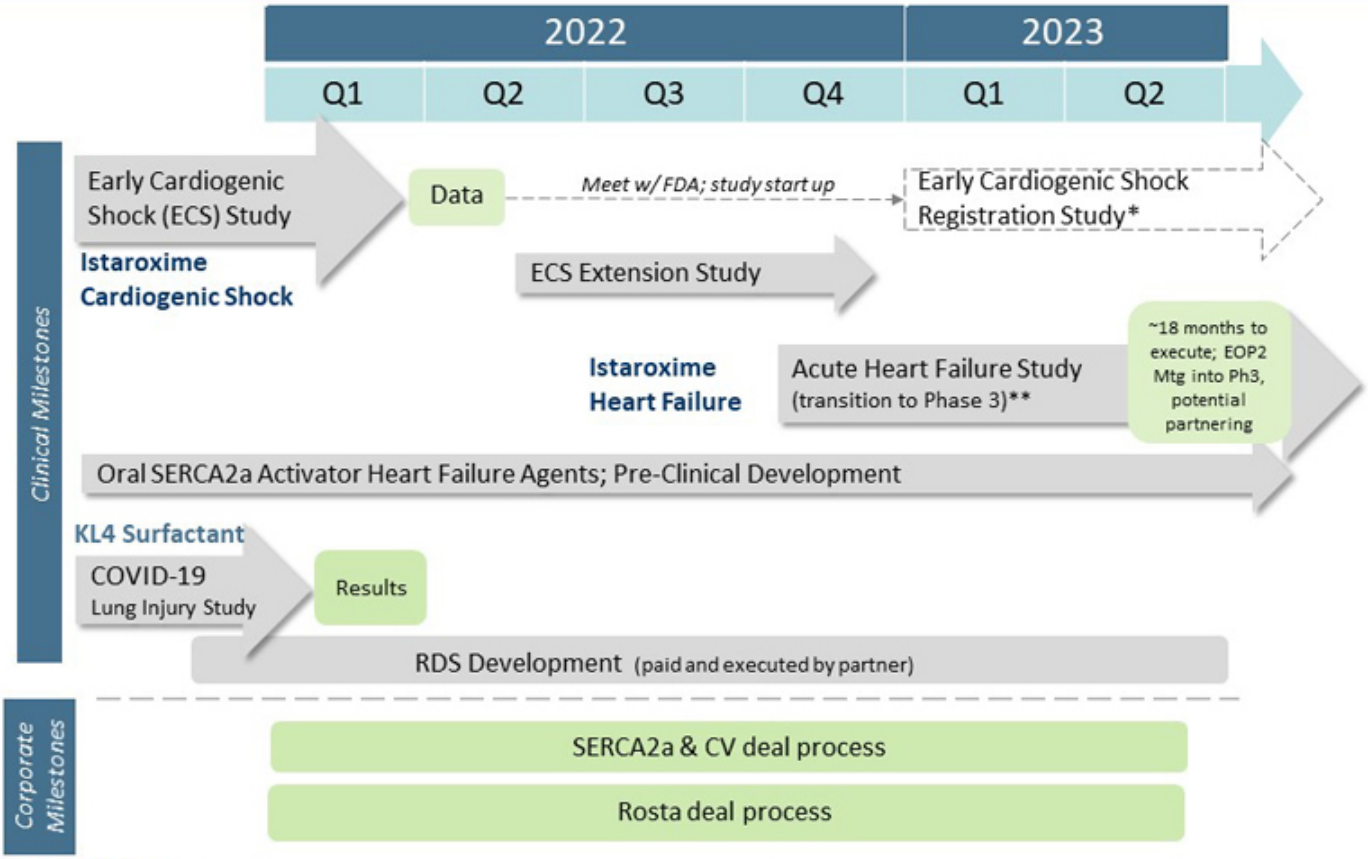
- **Highly experienced** management team and company leadership

Windtree Therapeutics Pipeline

	Lead Products	Pre-	Phase I	Phase II	Phase III	Next Milestone
FDA Fast Track Designation	**Istaroxime** (Acute Heart Failure)			Phase 2b		▪ Study start up ongoing for second Phase 2b clinical trial in ~300 patients targeted to start once clinical trial operations are fully funded
Potential for Breakthrough designation	**Istaroxime** (Early Cardiogenic Shock)			Phase 2		▪ Completed enrollment in international clinical study in early cardiogenic shock; Data expected April 2022
	Oral SERCA2a Activators (Chronic HF; potentially HFpEF)			Preclinical		▪ Chronic and Acute Heart Failure ▪ Target for collaboration/partnership
FDA, EMA Orphan Drug for RDS	**KL4 Surfactant – COVID 19** (COVID 19 Pilot; Open-Label)			Phase 2		▪ Study completed; Results expected March 2022
FDA Fast Track Designation, Orphan Drug	**AEROSURF** (KL4 surfactant Drug/Device Tx for Preterm Infants with RDS)			Phase 2b		▪ Respiratory Distress Syndrome (RDS) development to be funded and executed by licensee
	Rostafuroxin (Genetically Associated HTN)			Phase 2b		▪ Out-licensing opportunity

Strategy for Value Creation

Planned Milestones

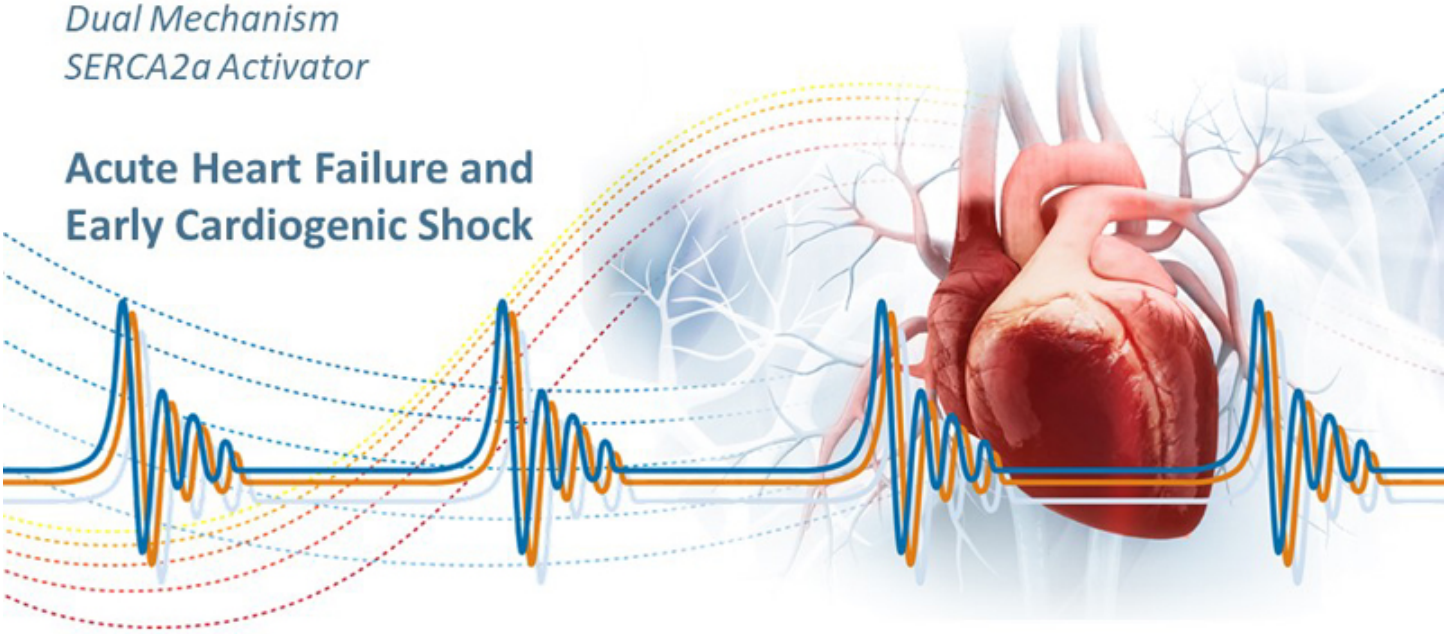


*study initiation pending positive data, regulatory input and adequate funding
**study initiation pending adequate funding

Istaroxime

Dual Mechanism
SERCA2a Activator

Acute Heart Failure and Early Cardiogenic Shock



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Heart Failure – Large, Growing Market But Underserved

The prevalence and mortality of heart failure is high and increasing

- 6M U.S., 20M+ worldwide patients
- #1 cause of U.S. hospitalization in patients > 65 years old;
  - > 1.3M admissions annually (U.S.) ~1.5M admissions annually (E.U.)
- In-patient mortality up to 7%; 30-day mortality can exceed 10%
- Most expensive of the Medicare diagnoses; U.S. hospitals >$18B annually
- There has not been meaningful 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

Acute Heart Failure – Significant Unmet Clinical Need

- **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 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**

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

Istaroxime – Novel First-in-Class Therapy

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

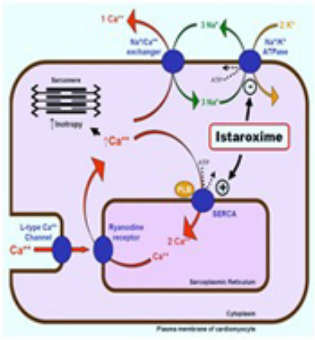
Dual Mechanism of Action

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



WINDTREE THERAPEUTICS

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

- 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

- Primary: E/e' (echocardiographic assessment of PCWP) was significantly improved by both doses
- Heart rate decreased and stroke volume increased
- Istaroxime maintained / increased systolic blood pressure
- Renal function tended to improve
- No evidence for increased risk of arrhythmia or increases in troponin
- Generally well tolerated (nausea and infusion site discomfort were most common AEs)

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

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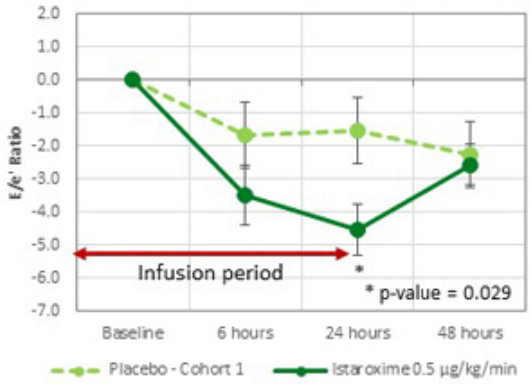
Primary Endpoint Achieved

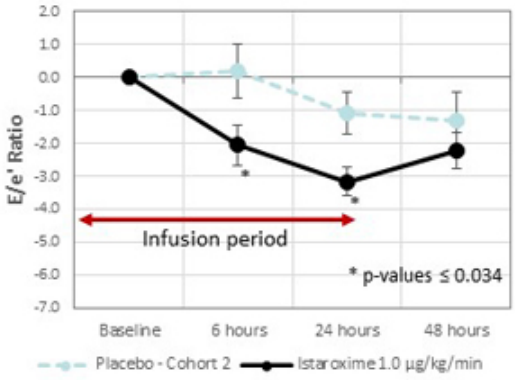
Significant Changes in E/e' Ratio(1) and Stroke Volume

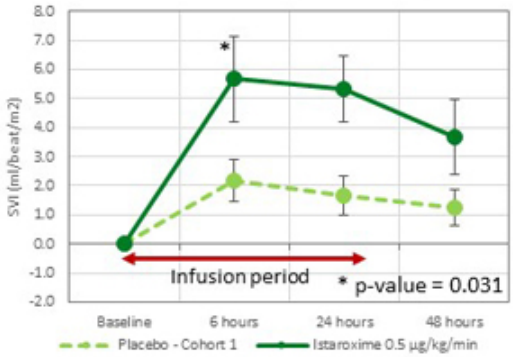
istaroxime 0.5 µg/kg/min vs. placebo



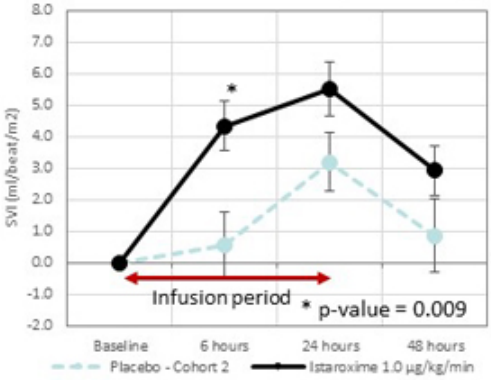
E/e'

istaroxime 1.0 µg/kg/min vs. placebo





Stroke Volume

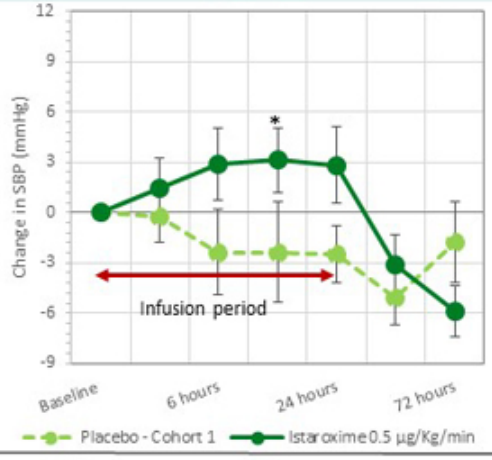


WINDTREE THERAPEUTICS

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

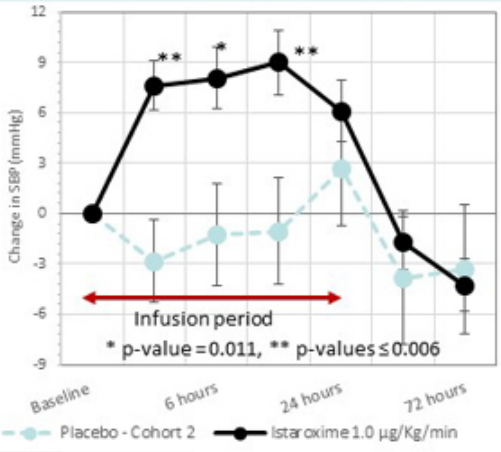
Systolic Blood Pressure Increased During Treatment and Renal Function Tended to Improve

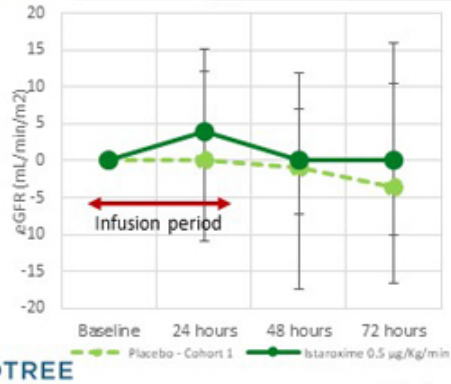
istaroxime 0.5 µg/kg/min vs. placebo



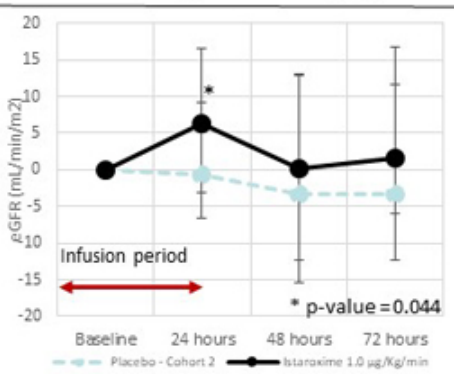
Systolic Blood Pressure (SBP)

istaroxime 1.0 µg/kg/min vs. placebo





GFR (Renal Function)

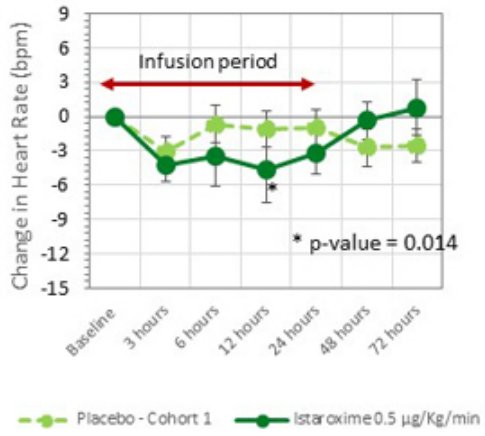


WINDTREE THERAPEUTICS

Data shown as means and standard errors

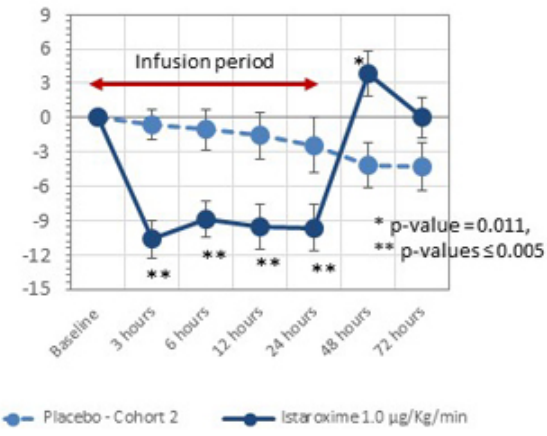
Heart Rate Decreased and No Increases in Cardiac Troponins

istaroxime 0.5 µg/kg/min vs. placebo



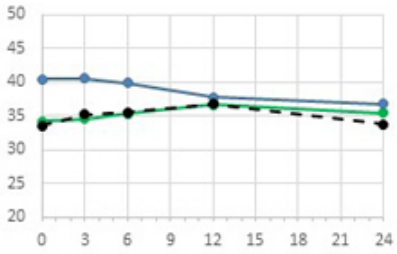
Heart Rate

istaroxime 1.0 µg/kg/min vs. placebo

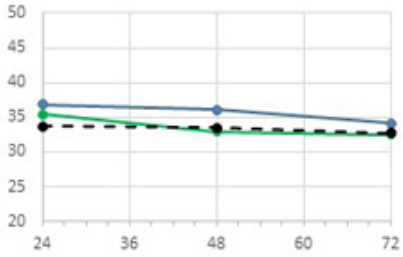


Cardiac TnT (Myocardial Damage)

cTnT – 0 to 24 hours



cTnT – 24 to 72 hours



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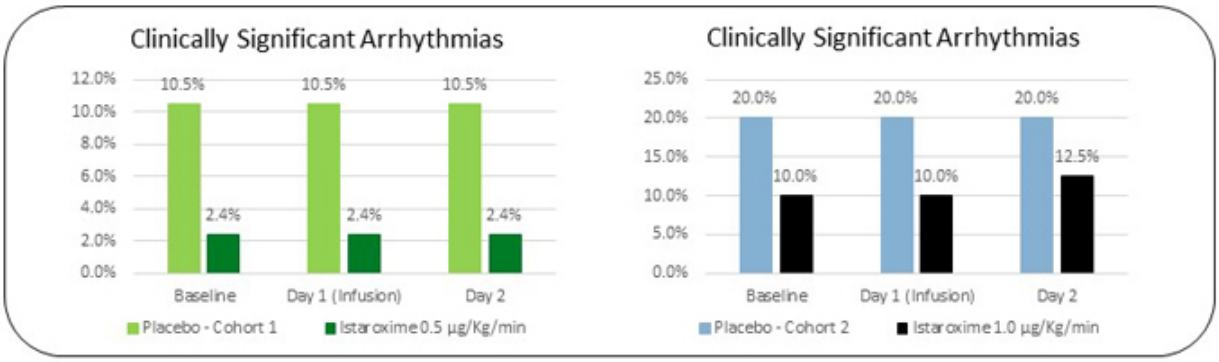
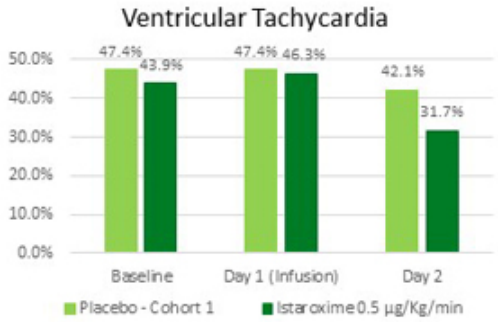
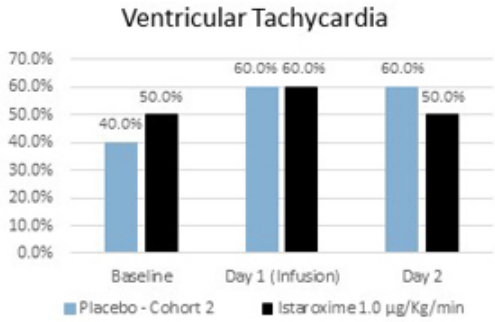
Favorable Profile Observed with 24-hour Holter Monitoring







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

Istaroxime – Acute Heart Failure

Next Steps

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**

I**ncrease infusion time** to >24 hours in pursuit of dose optimization

- Executing FDA required 14-day dog toxicology study to support longer dosing

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

Study start up underway with initiation pending adequate funding; ~18 months to execute

WINDTREE THERAPEUTICS

* Estimates

Istaroxime

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]

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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

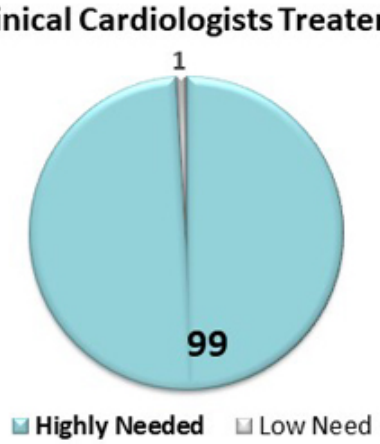
Early Cardiogenic Shock Treatment

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**

Market Research[1]

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

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

Early Cardiogenic Shock Treatment

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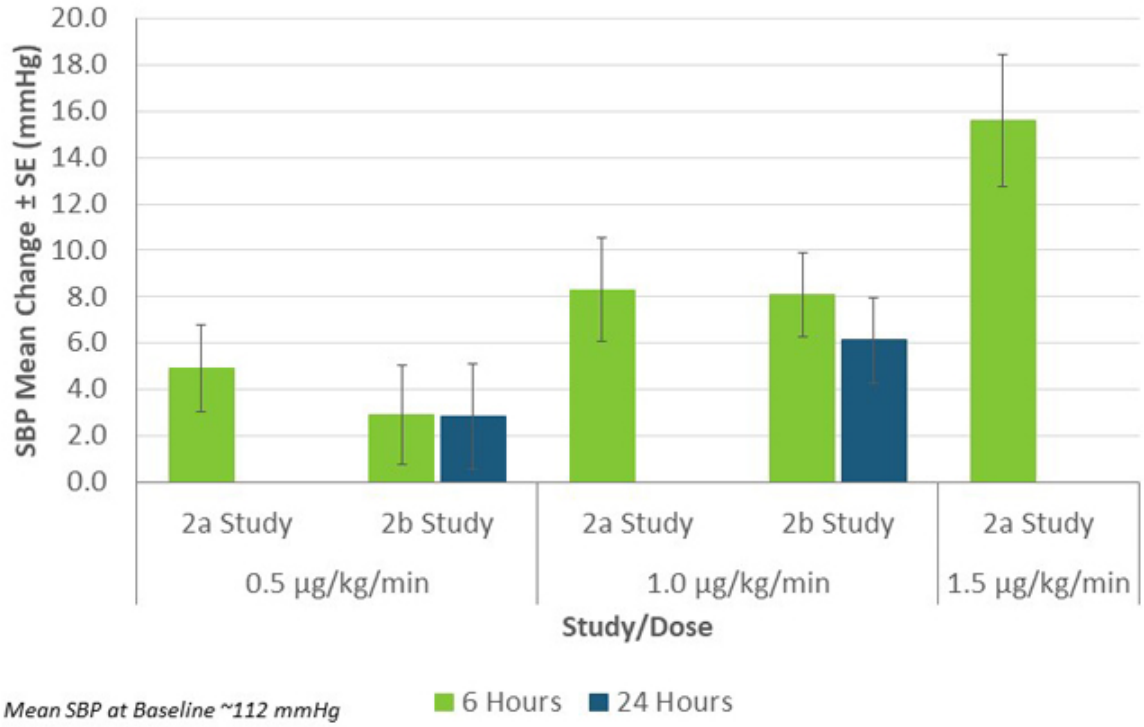
1) Kosaraju A, Hai O. Cardiogenic Shock. [Updated 2019 Jan 25]. In: https://www.ncbi.nlm.nih.gov/books/NBK482255/
CSRC Think Tank - July 24, 2019
2) Senatore et al., Am J Cardiovasc Drugs, February 2019, Volume 19, Issue 1, pp 11–20 (https://doi.org/10.1007/s40256-018-0297-9)

Changes in SBP – Phase 2a and 2b Dose Groups

Istaroxime Has Potential to Improve Blood Pressure and Organ Perfusion



Mean SBP at Baseline ~112 mmHg

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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 patient global study in early cardiogenic shock (SBP 75-90mmHg) with AHF

1.0 - 1.5µg/kg/min target dose for 24 hours

- Primary endpoint is SBP AUC at 6 hours
- Other measures include arrhythmias, SBP AUC at 24 hours, echo measures, etc.

Timing: Enrollment Complete - Data expected in April 2022

Clinical Objectives / "What Good Looks Like":

1. Rapid, meaningful improvement in SBP (to ≥90mmHg)
2. Improved systolic and diastolic cardiac function
3. Acceptable safety profile
   - without increasing heart rate, arrhythmias or renal damage
4. Support registration program
   - possible accelerated pathway

SEISMiC Extension Study (amendment to the ECS study)

Assuming 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 ~21 patients (2:1 randomization) with SBP between 75-115mmHg conducted in sites in the US, Europe and LATAM

48-hour infusions of 1.0µg/kg/min titrated down, or not, versus control

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

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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

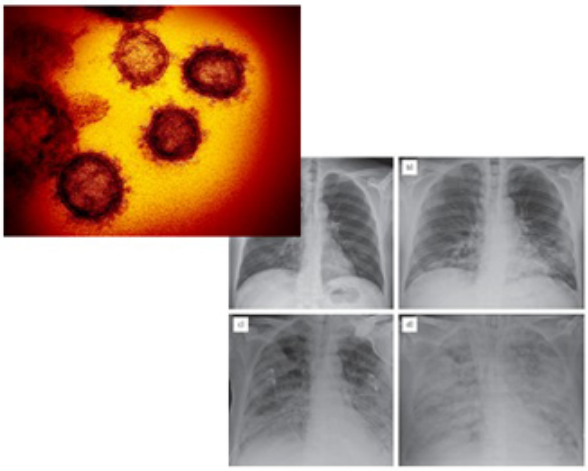
Summary
Potential to Create Value

- Acute heart failure – large market with significant unmet need
  - Istaroxime appears to be the only drug in Phase 2 or Phase 3 development for AHF treatment
- Istaroxime AHF– dual-mechanism therapy with positive Phase 2a and 2b trial outcomes:
  - ✓ Improved cardiac function
  - ✓ Uniquely improved SBP and renal function
  - ✓ Favorable safety profile compared to existing therapies
- Istaroxime Early Cardiogenic Shock study addresses a significant unmet need. Study enrollment is complete with data expected in April 2022
- Early Cardiogenic Shock indication may create a valuable, additional program and option for the company. Pathway to approval and launch may be both faster and cost less with a scale fitting of Windtree with an indication that is complimentary to AHF
- Next generation, oral SERCA2a activators in early development create a multi-asset, chronic and acute heart failure platform

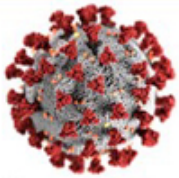
Lyo Lucinactant

Synthetic KL4 Surfactant

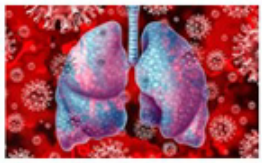
Lung Injury in COVID-19 Patients



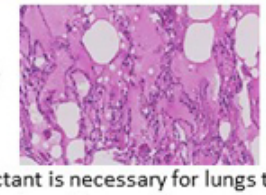
COVID-19 and ARDS Have Significant Negative Impact on Surfactant-Related Lung Function



Uses angiotensin-converting enzyme 2 (ACE2) for entry into host cells



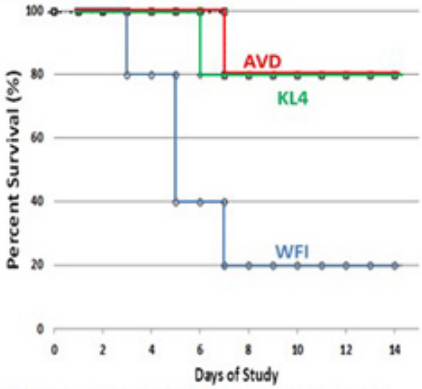
ACE2 is surface molecule on alveolar Type 2 lung cells – the source of surfactant



Surfactant is necessary for lungs to stay inflated and for proper gas exchange; Type 2 cell damage results in impaired surfactant production

Increased likelihood of mechanical ventilation

- COVID-19 infection can cause serious lung injury resulting in acute respiratory distress syndrome (ARDS) – condition with high mortality and no approved drug therapies, where **surfactant abnormalities** are an important factor
- Recent publications suggest that **lung fibrosis** and severe **interstitial changes** occur in COVID-19 patients who developed ARDS (1, 2, 3)
  - Changes resemble those seen in **premature infants** who are initially ventilated due to RDS and later develop bronchopulmonary dysplasia (BPD)
- **KL4 surfactant** significantly reduced mortality in a pre-clinical study of highly pathogenic avian (H5N1) influenza



KL4 = aerosolize KL4 surfactant, WFI = aerosolized water (control), AVD = aerosolized KL4 surfactant + antiviral

1) Bernheim, A., X. Mei, et al. (2020). "Chest CT Findings in Coronavirus Disease-19 (COVID-19): Relationship to Duration of Infection." Radiology: 200463.
2) Hosseiny, M., S. Kooraki, et al. (2020). "Radiology Perspective of Coronavirus Disease 2019 (COVID-19): Lessons From Severe Acute Respiratory Syndrome and Middle East Respiratory Syndrome." American Journal of Roentgenology: 1-5.
3) Song, F., N. Shi, et al. (0). "Emerging 2019 Novel Coronavirus (2019-nCoV) Pneumonia10.1148/radiol.2020200274." Radiology 0(0): 200274

Phase 2 study of Lucinactant (KL4 Surfactant) for Treatment of COVID-19

Objective: Demonstrate safe and tolerable surfactant administration and changes in physiological parameters in COVID-19-associated lung injury and ARDS

- Open-label, single arm study in 20 patients from 4 US sites and up to 4 sites in Latin America

- Dosing through the endotracheal tube, target 80 mg TPL/kg; repeat dosing based on improvement in oxygenation

- Outcome measures include:
  - Safety and tolerability of both drug and its administration
  - Physiologic response: Oxygenation Index (OI)

Status: Enrollment Complete

Results expected in March 2022

Seek non-dilutive partnership / grant funding to advance KL4 platform

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AEROSURF

Synthetic KL4 Surfactant with Proprietary Aerosol Delivery System

Respiratory Distress Syndrome (RDS)

Respiratory Distress Syndrome (RDS)

Current Treatment Pathways

- Surfactant helps keep lungs open between breaths and gas exchange
- Premature infants experience respiratory distress syndrome ("RDS") due to lungs lacking endogenous surfactant
- Physicians must choose between invasive surfactant delivery with known, significant complications or non-invasive nasal continuous positive airway pressure (nCPAP) alone (that often fails without surfactant)

	AEROSURF	Current Treatment	
	Non-Invasive Synthetic Surfactant	**Invasive Surfactant (~40%)**	**nCPAP Only (~60%)**
Surfactant	▪ Proprietary Synthetic KL4 surfactant[1]: – Structurally similar to human lung surfactant	▪ Animal derived	▪ None
Method of Delivery	▪ Proprietary aerosol delivery system (ADS) with nCPAP	▪ Intubation usually in combination with mechanical ventilation	▪ Nasal prongs
The AEROSURF Difference	▪ **Timely surfactant therapy delivered non-invasively to avoid potential complications** ▪ **Improves respiratory parameters** ▪ **Potential for decreased nCPAP failures and decreased need for invasive intubation and decreased rates of bronchopulmonary dysplasia (BPD)**	▪ **Timely therapy, but exposure to known significant complications associated with invasive intubation**	▪ **Avoid exposure to significant complications** ▪ **Foregoing surfactant treatment results in notable nCPAP failure rate and intubations**

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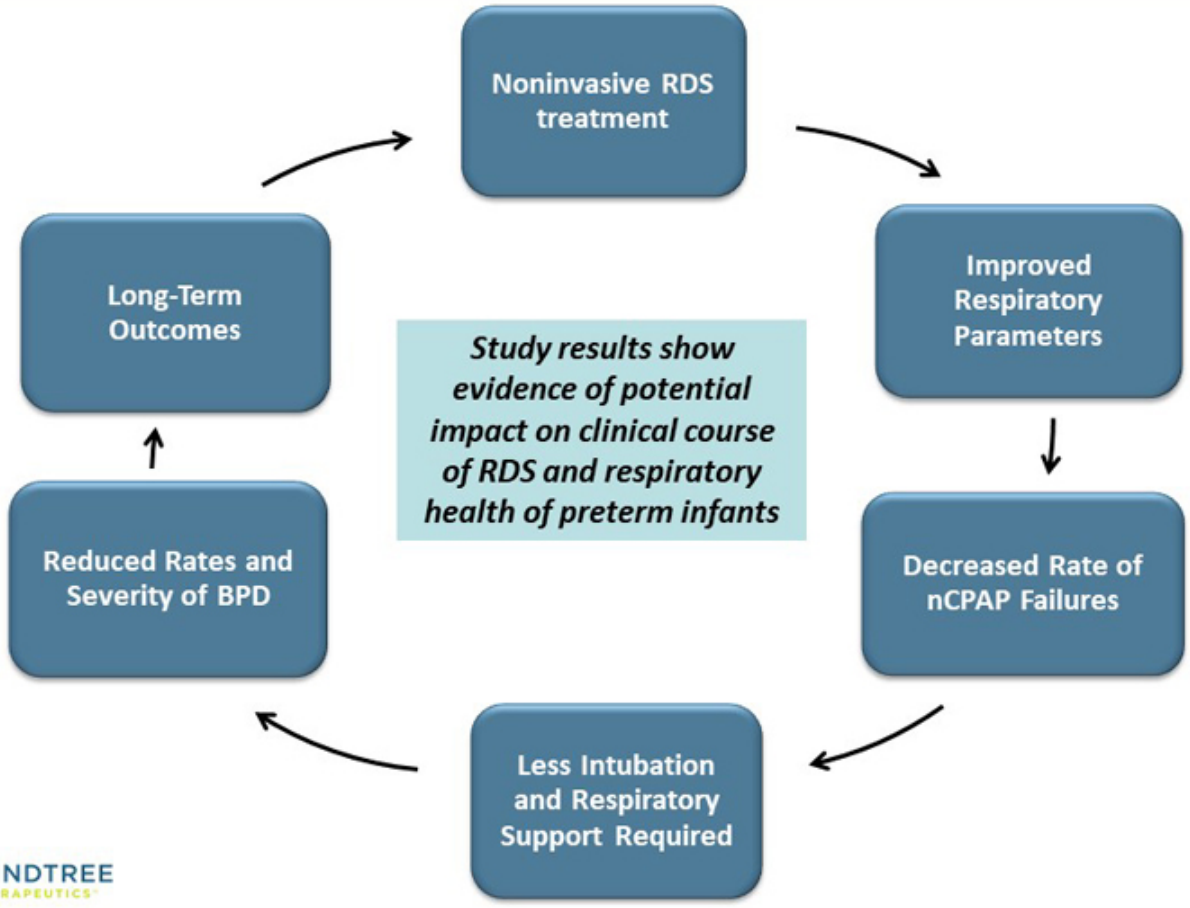
1) Liquid KL4 surfactant for RDS approved by the FDA. Lyophilized KL4 currently being developed for AEROSURF

AEROSURF® – Potential to Impact the Clinical Course of RDS

Building Evidence From Nearly 400 Patients Studied



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AEROSURF® Program Evolution and Strategy

Mitigating Risks and Strengthening Our Approach

Program Evolution

✓ Completed three Phase 2a and 2b trials

✓ Demonstrated efficacy in reducing nCPAP failure, need for intubation and BPD with a generally positive safety profile

✓ Transitioned to the newly-developed ADS

Program Strategy

1. Execute small (n=~80 - 90) Bridging Study to transition to EOP2/Phase 3:
   - Demonstrate that new ADS works and supplement Phase 2 data
   - Optimize dosing with more drug and shorter repeat intervals
2. Leverage partnership with Lee's to execute in Asia (the largest market) and fund the above study in non-dilutive manner
   - May allow Windtree to do more investment across adult applications (i.e. lung injury, acute cardiovascular programs)
3. Continue business development for potential additional partnerships and licensing ex-Asia

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Financial Summary & Capitalization as of September 30, 2021

- Cash & Equivalents of ~$24.5 million

Securities	Common Equivalents as of November 10, 2021
Common Stock	28,268,926
Options (WAEP $10.03)	3,402,666
Warrants (WAEP $9.43)	16,628,802
Fully Diluted Equivalents	48,300,394

Strategy for Value Generation

WINDTREE THERAPEUTICS™

- **Strong Clinical Execution to Deliver Milestones**: Execute well our late-stage clinical programs for achievement of milestones and news flow that may be growth catalysts
- **Transactions**:
  - Secure focused BD transactions for deal revenue and non-dilutive financial support of clinical development
  - Progress heart failure platform to an attractive and valuable position for global partnership (while retaining US co-promotion rights)
- **Optimization**: Bring in new, well-suited development opportunities and transactions

www.windtreetx.com

Windtree Therapeutics

"Striving to Deliver Hope for a Lifetime!"

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Appendix

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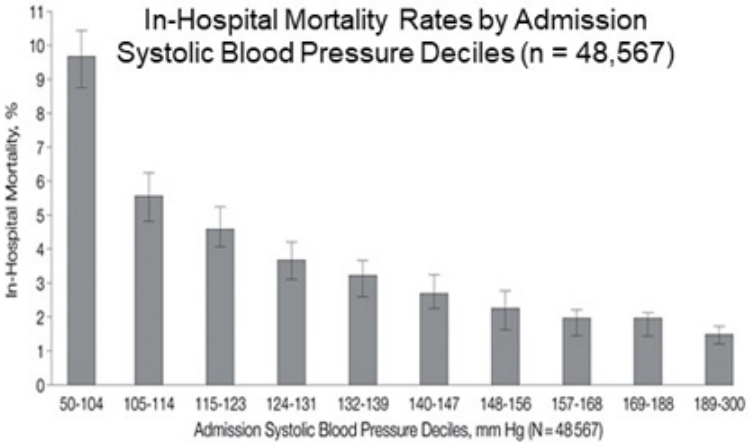
Acute Heart Failure

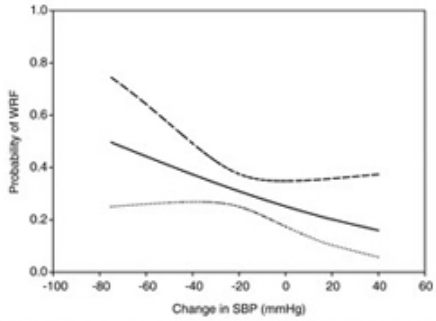
Significant Healthcare Issue with Significant Unmet Clinical Need

- **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[1]
  - There is a direct relationship between early drop in SBP and worsening renal function in acute heart failure[2]



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

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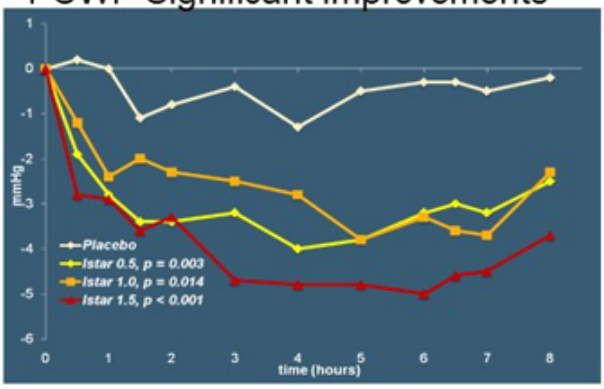
1) ADHERE Registry, n=48,567; JAMA 2006
2) European Journal of Heart Failure; Voors, PRE-RELAX AHF Study; 2011; 13

Istaroxime Phase 2a (HORIZON-HF) Study

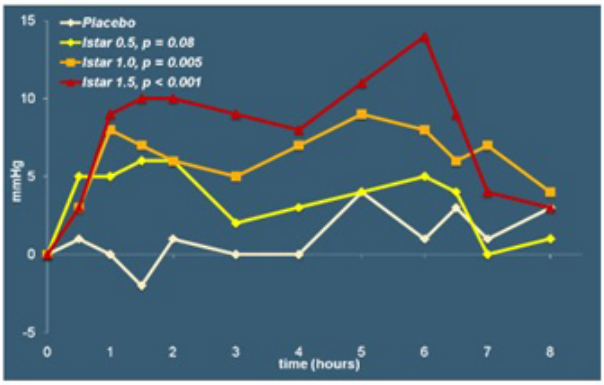
- Multicenter, double blind, placebo-controlled, doses 6-hour infusion of istaroxime 0.5, 1.0, 1.5 ug/kg/min, conducted in the EU
- Hospitalized with AHF, with criteria including:
  - LVEF ≤ 35%
  - SBP 90-150 mmHg
- N=120 (30/group)
- Significant improvement in PCWP, SBP, heart rate was lower. Istaroxime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

Primary Endpoint:

PCWP Significant Improvements



Dose-dependent Increase in SBP



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Istaroxime Phase 2b Adverse Events

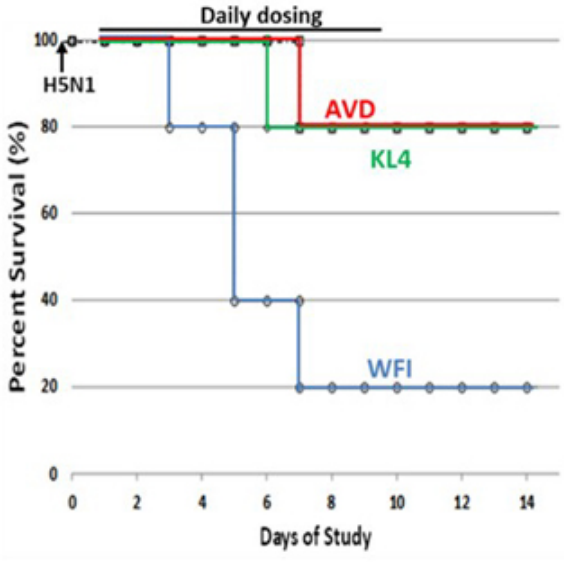
Event	Pooled placebo (n=39)	istaroxime 0.5 mg/Kg/min (n=41)	istaroxime 1.0 mg/Kg/min (n=40)
All adverse events	23 (59.0%)	31 (75.6%)	33 (82.5%)
Adverse events leading to discontinuation	1 (2.6%)	-	4 (10.0%)
Serious adverse events	2 (5.1%)	2 (4.9%)	6 (15.0%)
Cardiac death	-	-	1 (2.5%)
Cardiogenic shock	-	-	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 (35.0%)
Infusion site pain/inflammation	-	20 (48.8%)	13 (32.5%)

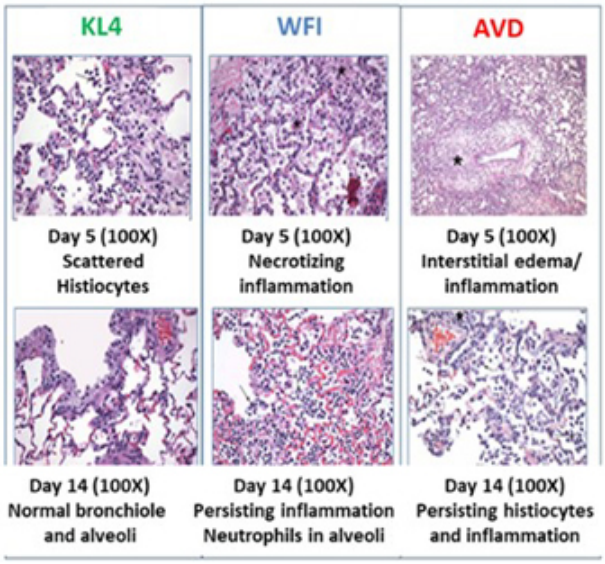
Note: data shown as n° patients (%) - patients can have more than one event during the 30-day follow up period
* Same patient who then died, and 1 additional death occurred at Day 31 (cardiac death) outside the 30 day window
† Adverse Drug Reactions are AEs related to study drug
††Most common - arrhythmia, atrial fibrillation, cardiac failure, ventricular tachycardia
‡ Most common - abdominal pain, nausea, vomiting, diarrhoea

KL4 Surfactant Significantly Reduced Mortality in a Pre-Clinical H5N1 Study

H5N1 Study – With and Without Anti-Viral Agent

- Ferrets Infected with highly pathogenic avian (H5N1) influenza
- Results in significant viral and inflammation related lung damage that is substantially ameliorated by KL4 surfactant treatment





KL4 = aerosolize KL4 surfactant, WFI = aerosolized water (control), AVD = aerosolized KL4 surfactant + antiviral

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Evidence of KL4 Surfactant Potential Utility in COVID-19

Demonstrated Utility Across Various Respiratory Distress

We have been evaluating the applicability of KL4 surfactant for multiple etiologies of lung injury as well as pandemic influenza long before the COVID-19 pandemic

Demonstrated Utility of KL4	
Extensive Studies in Acute Lung Conditions:	▪ 13 studies for intratracheal administration including RDS, BPD, acute hypoxemic respiratory failure and adults with ARDS ▪ 2,148 patients enrolled | 1,028 treated ▪ Aerosolized KL4 surfactant studied in 366 subjects enrolled, 223 subjects treated
SARS and Subsequent Support for Acute Lung Injury Studies	▪ ~$10M of NIH support for clinical and non-clinical programs including lung protection studies involving viral infections with H1N1 and RDS ▪ CEO testified before congressional committee regarding KL4 for the treatment of SARS
American Thoracic Society Presentation	▪ KL4 surfactant has the potential to be employed to protect the lung and reduce mortality in patients exposed to highly pathogenic influenza as well as against pandemic strains

In May 2018 data from a preclinical animal model of a **highly pathogenic H5N1 viral** pneumonia was presented showing aerosolized KL4 surfactant reduced lung damage and improved overall survival

Respiratory Distress Syndrome (RDS)

Current Treatment Pathways

Premature infants experience RDS due to underdeveloped lungs lacking endogenous surfactant. Surfactant helps keep lungs open between breaths and proper gas exchange

Initial treatment options include invasive and noninvasive methods:

Surfactant therapy + Invasive mechanical ventilation (IMV)	VS.	**nCPAP support until endogenous surfactant production**
• Animal-derived surfactant • Delivered via intubation, usually in combination with mechanical ventilation		• Noninvasive nasal delivery of continuous positive airway pressure (nCPAP) • Supports breathing

TRADE-OFFS

Timely therapy delivery vs. Exposure to known significant complications

Avoid exposure to significant complications vs. Foregoing surfactant treatment results in notable nCPAP failure rate

Ultimately, more than 50% of RDS infants are intubated and ventilated

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Source: Windtree and third-party market research

Windtree Technology Platform – AEROSURF®

Proprietary Synthetic KL4 Surfactant

+

Proprietary Innovative Aerosol Delivery System (ADS)

Structurally similar to human lung surfactant

Liquid KL4 surfactant (intratracheal instillate) for RDS **approved by the FDA**

Lyophilized KL4 surfactant currently being developed for **AEROSURF**

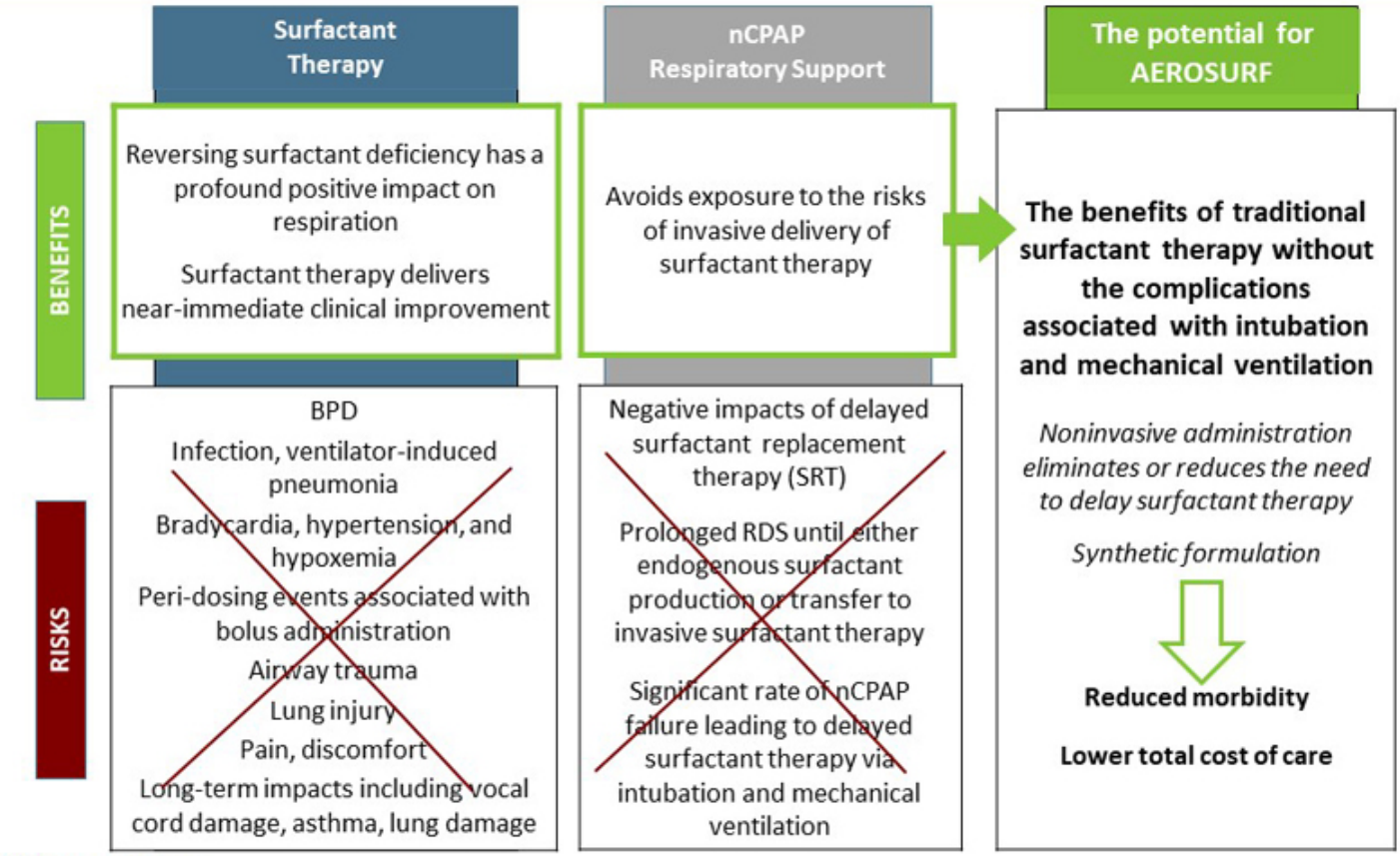
Utilizing pressure and heated capillary has demonstrated ability to **aerosolize KL4 surfactant**

Controlled, effective and reproducible performance validated in studies

- KL4 surfactant has been shown to improve lung function in premature infants, resulting in decreased nCPAP failures and need for invasive intubation
- KL4 surfactant also has anti-inflammatory and other potentially positive attributes

WINDTREE THERAPEUTICS

Transformative Potential of AEROSURF®



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Business Development Focus

We are actively engaged in discussions with multiple companies with a proactive focus as follows:

Short-term

- Cardiovascular Partner – China
- Pure SERCA2a Pharma Partner – Global
- AEROSURF® / KL4 Licensing ex-Asia

Mid-term (Data & EOP2)

- Heart Failure Portfolio Partner – Global
- Rosta Out-License - Global

Long-term (Strategy)

- Portfolio Optimization and Expansion
- Retained US Co-Promo Rights

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