

**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 31, 2022

Windtree Therapeutics, Inc.

(Exact name of registrant as specified in its charter)

Delaware
(State or other jurisdiction of
incorporation or organization)

000-26422
(Commission
File Number)

94-3171943
(I.R.S. Employer
Identification No.)

2600 Kelly Road, Suite 100, Warrington, Pennsylvania
(Address of principal executive offices)

18976
(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.



Windtree Therapeutics Reports Fourth Quarter and Year-End 2021 Financial Results and Provides Key Business Updates

WARRINGTON, PA – March 31, 2022 – Windtree Therapeutics, Inc. (NasdaqCM: WINT), a biotechnology company focused on advancing multiple late-stage interventions for acute cardiovascular and pulmonary disorders, today reported financial results for the fourth quarter and year ended December 31, 2021 and provided key business updates.

“This past quarter caps a very productive year for Windtree with progress towards multiple value-creating milestones, making for an exciting 2022. We are pleased to have successfully completed enrollment in our phase 2 study of istaroxime, our lead clinical program in early cardiogenic shock, and plan to announce topline data in April 2022. Cardiogenic shock represents a great opportunity for Windtree. It has significant unmet need, a potentially supportive scale and a regulatory pathway for development,” said Craig Fraser, President and Chief Executive Officer of Windtree. “We also continued with study preparations for additional development with istaroxime, including a planned extension to the early cardiogenic shock study and start-up activities for the next acute heart failure (AHF) trial that will build upon previous, positive phase 2 data.”

Key Business and Financial Updates

- Completed enrollment in the Company’s phase 2 study of istaroxime in early cardiogenic shock. The study is an international, randomized, double-blind, placebo-controlled study in 60 patients designed to assess the efficacy and safety of istaroxime in patients in early cardiogenic shock caused by heart failure and to support an intended pathway for development to an indication for use in cardiogenic shock. Topline data from the study is expected to be announced in April.
 - Advanced plans and preparation for an extension study to the early cardiogenic shock trial to characterize the physiology associated with longer and titrated istaroxime dosing as well as to increase understanding of the effects and potential benefits associated with SERCA2a activation, one of the key mechanisms of action for istaroxime.
 - Initiated and progressed study start-up activities to continue the development of istaroxime for the treatment of AHF with an additional phase 2b clinical trial that builds upon previous positive phase 2a and phase 2b results. Once fully funded, the study will focus on treating AHF 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 blood pressure while maintaining or improving renal function. This trial will also collect data on measures that may serve as primary endpoints in a phase 3 clinical trial, and will optimize the dosing regimen, potentially extending the infusion time beyond 24 hours.
 - Completed enrollment and announced results for the Company’s phase 2 single-arm study of lucinactant (KL4 surfactant) designed to evaluate the safety and tolerability of lucinactant delivered as a liquid via the endotracheal tube in 20 patients who were mechanically ventilated due to COVID-19 associated lung injury and severe ARDS. The study demonstrated that intratracheal administration of reconstituted lyophilized lucinactant was generally safe and well tolerated with stable to improved oxygenation and other physiological parameters after dosing, supporting the feasibility of this approach to develop a potential treatment for critically ill patients with ARDS due to COVID-19 and other causes.
-

- Announced U.S. Patent and Trademark Office issuance of istaroxime patent (U.S. Patent No. 1197869), covering the intravenous delivery of istaroxime for the treatment of AHF. The patent, titled “Istaroxime-Containing Intravenous Formulation for the Treatment of Acute Heart Failure,” covers longer infusion durations of istaroxime for improved outcomes in the treatment of AHF. The patent provides intellectual property protection through late 2039.

Select Financial Results for the Fourth Quarter ended December 31, 2021

For the fourth quarter ended December 31, 2021, the Company reported an operating loss of \$14.7 million, which includes non-cash expense of \$7.2 million related to the impairment of our rostafuroxin intangible asset, compared to an operating loss of \$7.0 million in the fourth quarter of 2020.

Research and development expenses were \$4.5 million for the fourth quarter of 2021, compared to \$3.5 million for the fourth quarter of 2020. The increase in research and development expenses is primarily due to an increase of \$0.9 million for the clinical activity and development of istaroxime in early cardiogenic shock and acute heart failure.

General and administrative expenses for the fourth quarter of 2021 were \$3.0 million, compared to \$3.4 million for the fourth quarter of 2020. The decrease in general and administrative expenses is primarily due to a decrease of \$0.6 million in professional fees.

The Company reported a net loss of \$13.1 million (\$0.46 per basic share) on 28.2 million weighted-average common shares outstanding for the quarter ended December 31, 2021, compared to a net loss of \$7.5 million (\$0.44 per basic share) on 16.9 million weighted average common shares outstanding for the comparable period in 2020.

Select Financial Results for the Year ended December 31, 2021

For the year ended December 31, 2021, the Company reported an operating loss of \$77.3 million, which includes non-cash expense of \$45.0 million related to the impairment of our rostafuroxin intangible asset, compared to an operating loss of \$30.3 million for the year ended December 31, 2020.

Research and development expenses were \$17.8 million for the year ended December 31, 2021, compared to \$15.4 million for the year ended December 31, 2020. The increase in research and development expenses is primarily due to (i) an increase of \$2.0 million for the recently completed clinical study of istaroxime for early cardiogenic shock and the continued development of istaroxime for AHF; and (ii) an increase of \$1.1 million related to personnel and non-cash, stock compensation expense; partially offset by (iii) a decrease of \$0.5 million related to the KL4 surfactant platform.

General and administrative expenses for the year ended December 31, 2021 were \$14.5 million, compared to \$14.9 million for the year ended December 31, 2020. The decrease in general and administrative expenses is primarily due to a decrease of \$0.8 million in severance costs and a decrease of \$0.4 million in professional fees, partially offset by an increase of \$0.7 million in non-cash, stock compensation expense.

The Company reported a net loss of \$67.6 million (\$2.73 per basic share) on 24.8 million weighted-average common shares outstanding for the year ended December 31, 2021, compared to a net loss of \$32.6 million (\$2.08 per basic share) on 15.7 million weighted average common shares outstanding for the comparable period in 2020.



As of December 31, 2021, the Company reported cash and cash equivalents of \$22.3 million. As of March 31, 2022, we believe that we have sufficient cash resources to provide runway into the first quarter of 2023.

Readers are referred to, and encouraged to read in its entirety, the Company's Annual Report on Form 10-K for the year ended December 31, 2021, which will be filed with the Securities and Exchange Commission on March 31, 2021, which includes detailed discussions about the Company's business plans and operations, financial condition, and results of operations.

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. 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 operations, including through disruption in supply chain or access to potential international clinical trial sites, and through 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.



Contact Information:

Monique Kosse
LifeSci Advisors
212.915.3820 or monique@lifesciadvisors.com

Media contact:

Andrew Mielach
LifeSci Communications
646.876.5868 or amielach@lifescicomms.com

+++++ Tables to Follow +++++



WINDTREE THERAPEUTICS, INC. AND SUBSIDIARIES
Consolidated Balance Sheets

(in thousands, except share and per share data)

	<u>December 31,</u> <u>2021</u>	<u>December 31,</u> <u>2020</u>
ASSETS		
Current Assets:		
Cash and cash equivalents	\$ 22,348	\$ 16,930
Prepaid expenses and other current assets	1,143	1,188
Total current assets	<u>23,491</u>	<u>18,118</u>
Property and equipment, net	1,011	924
Restricted cash	154	154
Operating lease right-of-use assets	2,381	917
Intangible assets	32,070	77,090
Goodwill	15,682	15,682
Total assets	<u>\$ 74,789</u>	<u>\$ 112,885</u>
LIABILITIES & STOCKHOLDERS' EQUITY		
Current Liabilities:		
Accounts payable	\$ 693	\$ 1,161
Accrued expenses	3,408	3,813
Operating lease liabilities - current portion	528	805
Loans Payable - current portion	294	352
Total current liabilities	<u>4,923</u>	<u>6,131</u>
Operating lease liabilities - non-current portion	2,071	201
Loans payable - non-current portion	-	2,423
Restructured debt liability - contingent milestone payments	15,000	15,000
Other liabilities	3,800	2,800
Deferred tax liabilities	7,114	16,778
Total liabilities	<u>32,908</u>	<u>43,333</u>
Stockholders' Equity:		
Preferred stock, \$0.001 par value; 5,000,000 shares authorized; 0 shares issued and outstanding at December 31, 2021 and 2020	-	-
Common stock, \$0.001 par value; 120,000,000 shares authorized at December 31, 2021 and 2020; 28,268,950 and 16,921,506 shares issued at December 31, 2021 and 2020, respectively; 28,268,926 and 16,921,482 shares outstanding at December 31, 2021 and 2020, respectively	28	17
Additional paid-in capital	830,231	790,277
Accumulated deficit	(785,324)	(717,688)
Treasury stock (at cost); 24 shares	(3,054)	(3,054)
Total stockholders' equity	<u>41,881</u>	<u>69,552</u>
Total liabilities & stockholders' equity	<u>\$ 74,789</u>	<u>\$ 112,885</u>



WINDTREE THERAPEUTICS, INC. AND SUBSIDIARIES
Consolidated Statements of Operations

(in thousands, except per share data)

	Year Ended December 31,	
	2021	2021
Expenses:		
Research and development	17,787	15,373
General and administrative	14,473	14,944
Loss on impairment of intangible assets	45,020	-
Total operating expenses	77,280	30,317
Operating loss	(77,280)	(30,317)
Other income (expense):		
Interest income	91	122
Interest expense	(114)	(125)
Other (expense), net	(320)	(2,246)
Total other (expense), net	(343)	(2,249)
Loss before income taxes	(77,623)	(32,566)
Deferred income tax benefit	9,987	-
Net loss	<u>\$ (67,636)</u>	<u>\$ (32,566)</u>
Net loss per common share		
Basic and diluted	\$ (2.73)	\$ (2.08)
Weighted average number of common shares outstanding		
Basic and diluted	24,760	15,654



Windtree Therapeutics

Company Overview

March 31, 2022

(NASDAQ: WINT)



Forward-Looking Statements

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

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

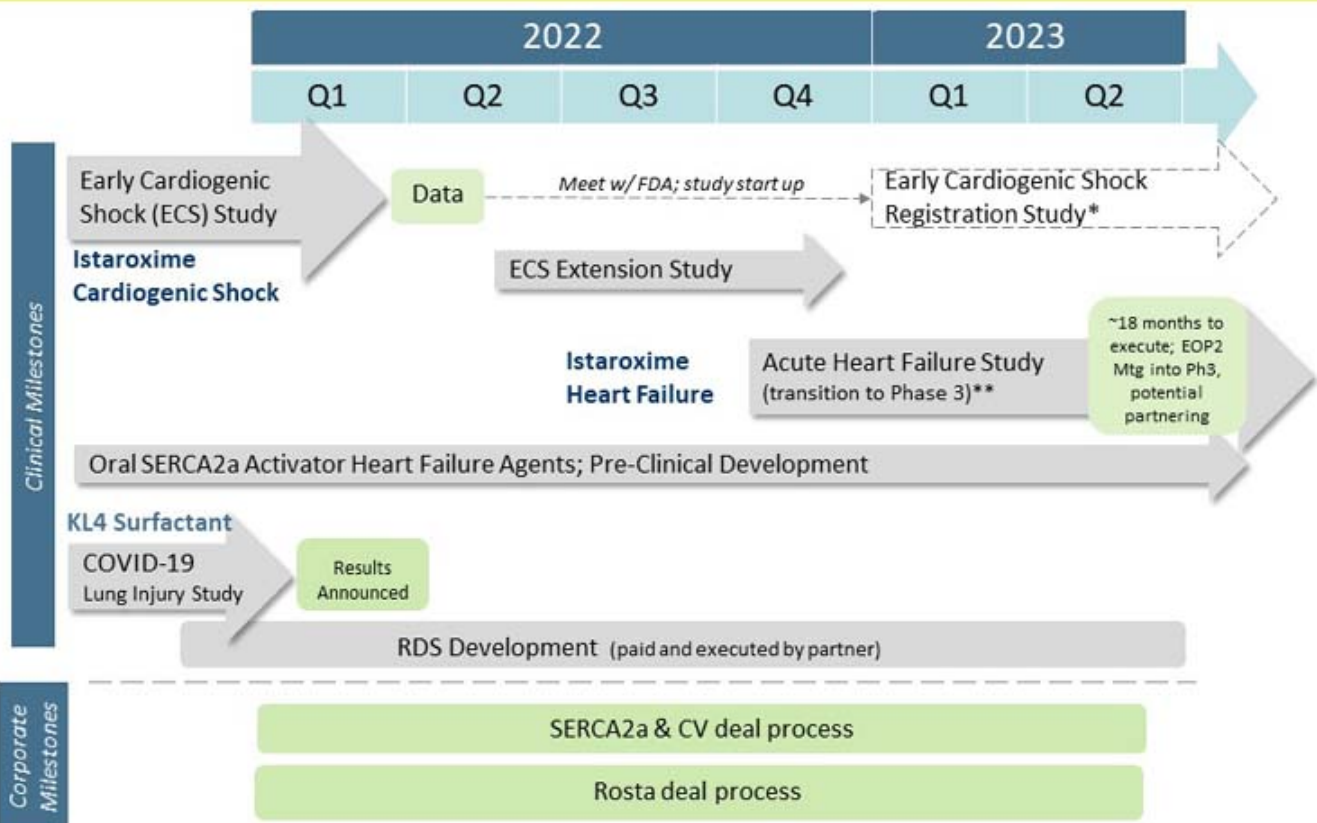
- ✓ **Highly experienced** management team and company leadership

Windtree Therapeutics Pipeline

	Lead Products	Phase of Development	Next Milestone
<i>FDA Fast Track Designation</i>	Istaroxime (Acute Heart Failure)	Phase 2b	<ul style="list-style-type: none"> Study start up ongoing for second Phase 2b clinical trial in ~300 patients targeted to start once clinical trial operations are fully funded
<i>Potential for Breakthrough designation</i>	Istaroxime (Early Cardiogenic Shock)	Phase 2	<ul style="list-style-type: none"> Completed enrollment in international clinical study in early cardiogenic shock; Data expected April 2022
	Oral SERCA2a Activators (Chronic HF; potentially HFpEF)	Preclinical	<ul style="list-style-type: none"> Chronic and Acute Heart Failure Target for collaboration/partnership
<i>FDA, EMA Orphan Drug for RDS</i>	KL4 Surfactant – COVID 19 (COVID 19 Pilot; Possible invasive Tx for RDS in neonates)	Phase 2	<ul style="list-style-type: none"> Study completed; Results presented March 2022
<i>FDA Fast Track Designation, Orphan Drug</i>	AEROSURF (KL4 surfactant Drug/Device Tx for RDS)	Phase 2b	<ul style="list-style-type: none"> Respiratory Distress Syndrome (RDS) development to be funded and executed by licensee
	Rostafuroxin (Genetically Associated HTN)	Phase 2b	<ul style="list-style-type: none"> Out-licensing opportunity

Strategy for Value Creation

Planned Milestones

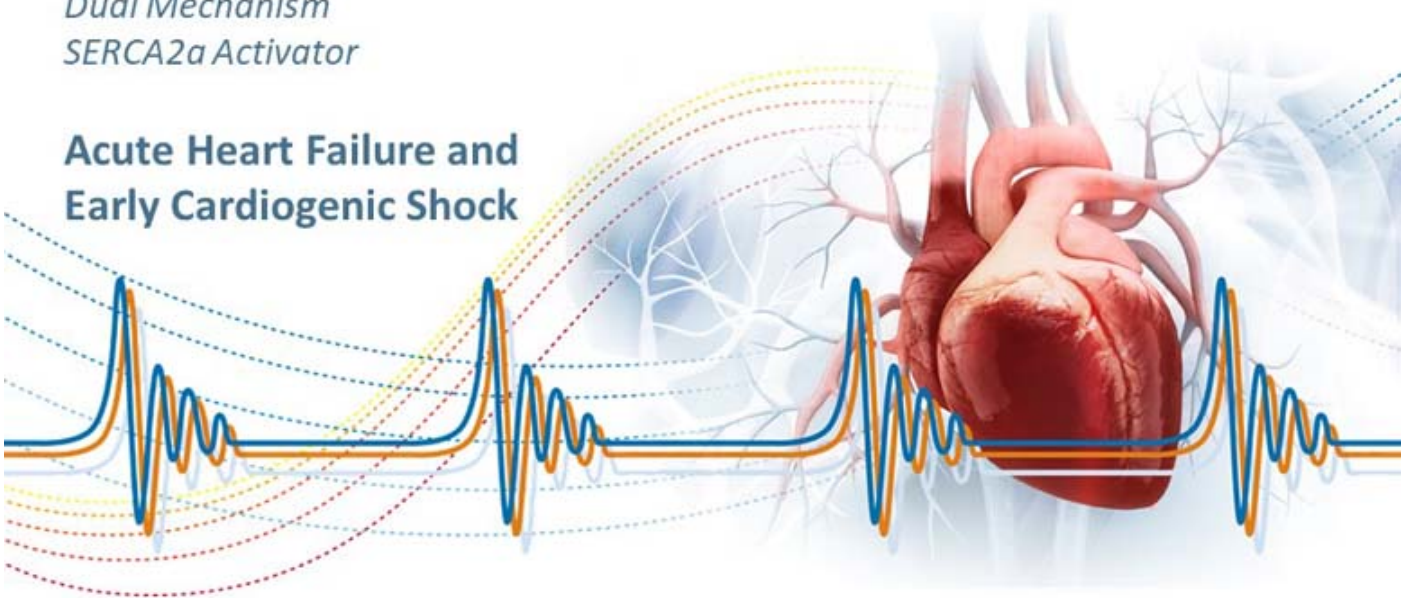


*study initiation pending positive data, regulatory input and adequate funding
 **study initiation pending adequate funding

Istaroxime

*Dual Mechanism
SERCA2a Activator*

**Acute Heart Failure and
Early Cardiogenic Shock**



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



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:**

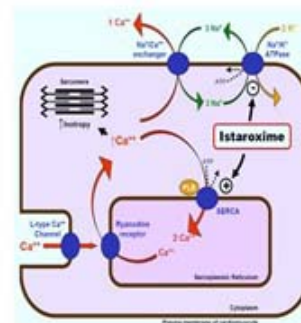
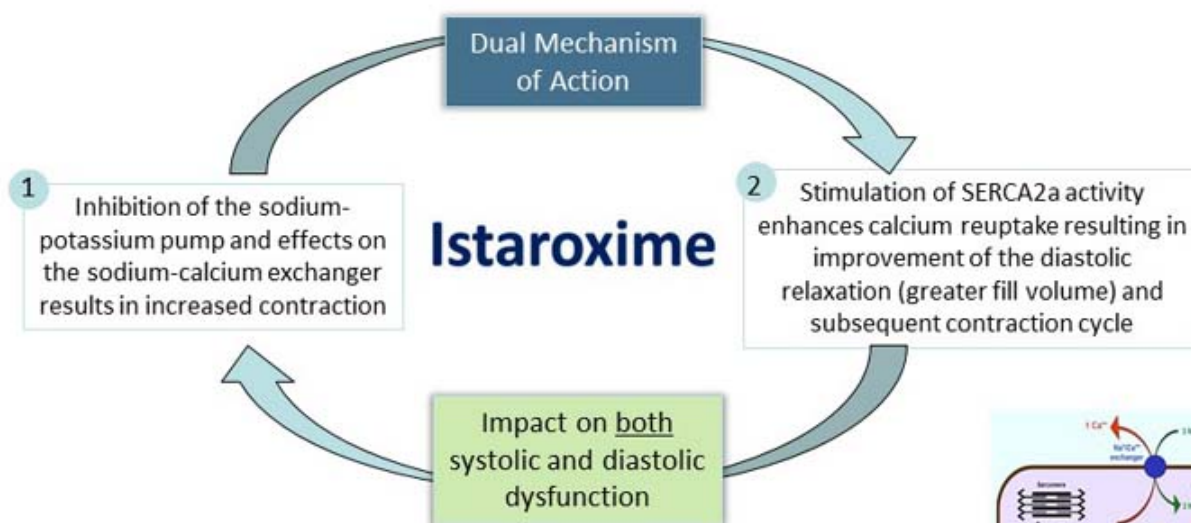
- Heart rhythm disturbances
 - Increased heart rate and myocardial oxygen demand
 - Decreased blood pressure
 - Potential damage to the heart muscle
 - Worsening renal function
 - Mortality
- **Patients with low blood pressure (SBP) and peripheral hypoperfusion are high risk, challenging patients who 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



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 $\mu\text{g}/\text{kg}/\text{min}$



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 \geq 40mg)

Dosing=
0.5, 1.0 $\mu\text{g}/\text{kg}/\text{min}$

24 hour
Infusion

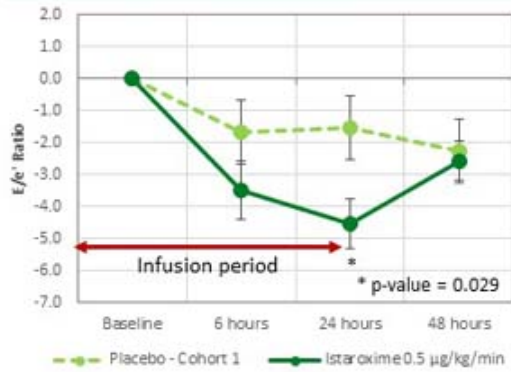
- Primary: E/e' (echocardiographic assessment of PCWP) was significantly improved by both doses
- Heart rate decreased and stroke volume increased
- Istaroxime maintained / increased systolic blood pressure
- Renal function tended to improve
- No evidence for increased risk of arrhythmia or increases 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

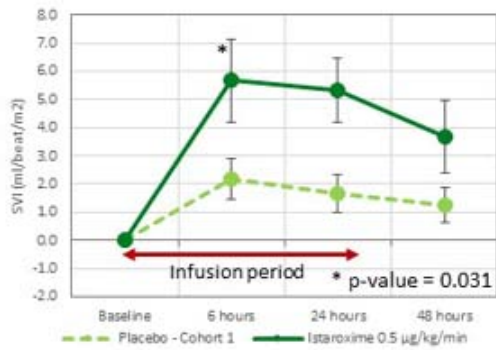
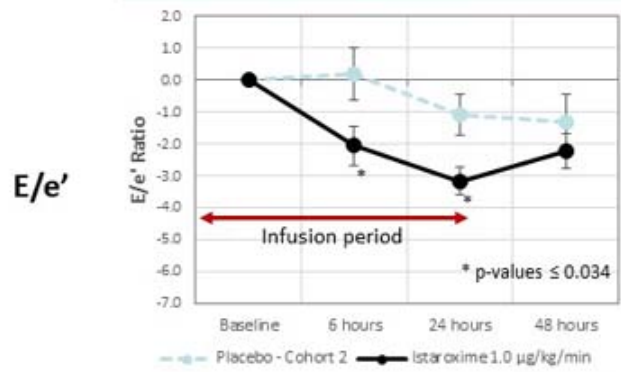
Primary Endpoint Achieved

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

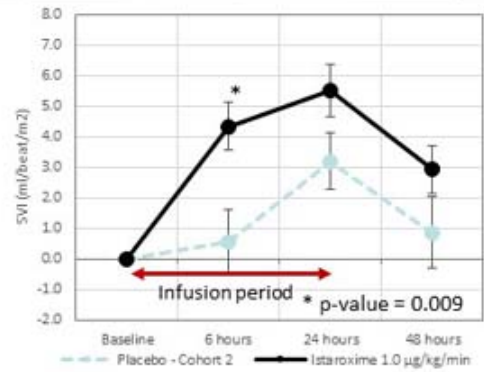
istaroxime 0.5 $\mu\text{g}/\text{kg}/\text{min}$ vs. placebo



istaroxime 1.0 $\mu\text{g}/\text{kg}/\text{min}$ vs. placebo



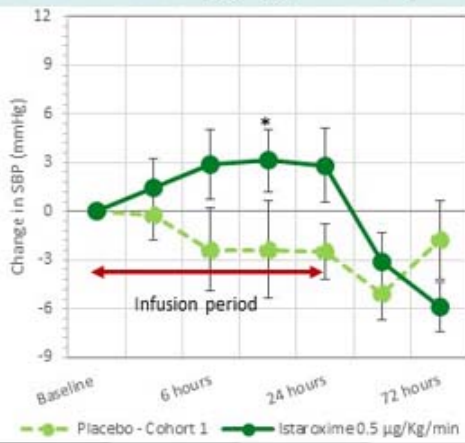
Stroke Volume



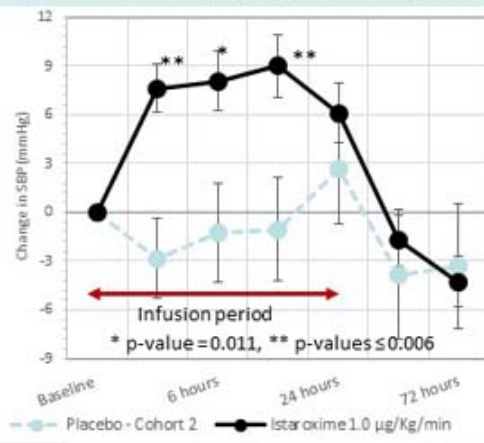
1) E/e' echocardiographic assessment of PCWP; Note: Data shown as means and standard errors

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

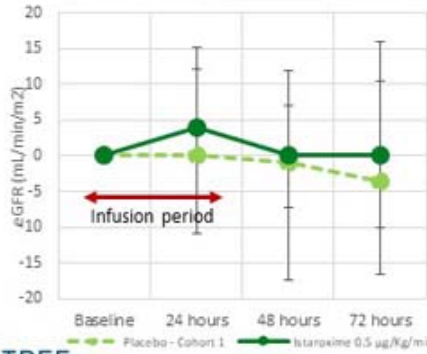
istaroxime 0.5 µg/kg/min vs. placebo



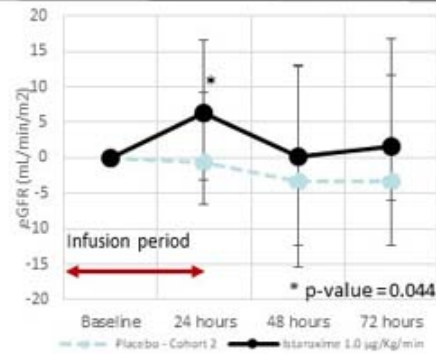
istaroxime 1.0 µg/kg/min vs. placebo



Systolic Blood Pressure (SBP)



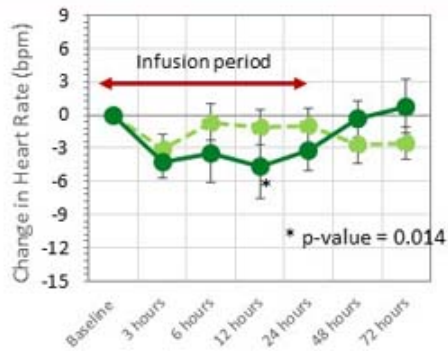
GFR (Renal Function)



Data shown as means and standard errors

Heart Rate Decreased and No Increases in Cardiac Troponins

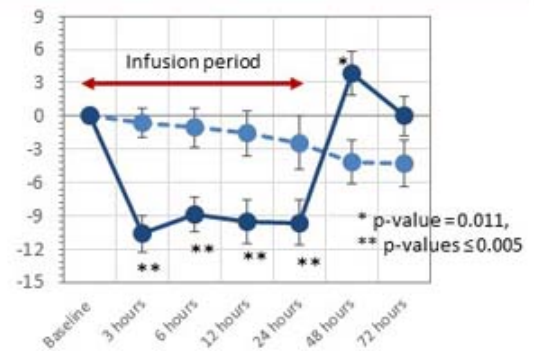
istaroxime 0.5 µg/kg/min vs. placebo



Placebo - Cohort 1 Istaroxime 0.5 µg/kg/min

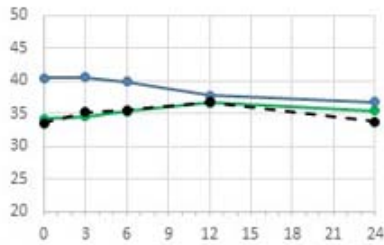
istaroxime 1.0 µg/kg/min vs. placebo

Heart Rate



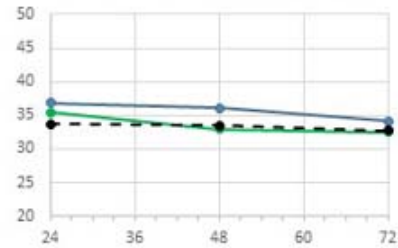
Placebo - Cohort 2 Istaroxime 1.0 µg/kg/min

cTnT – 0 to 24 hours

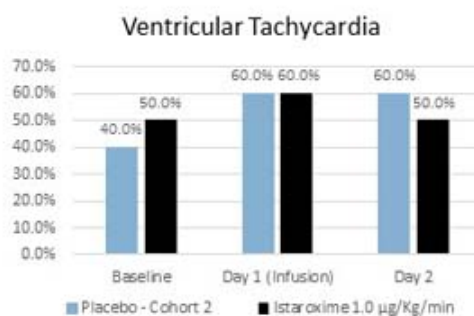
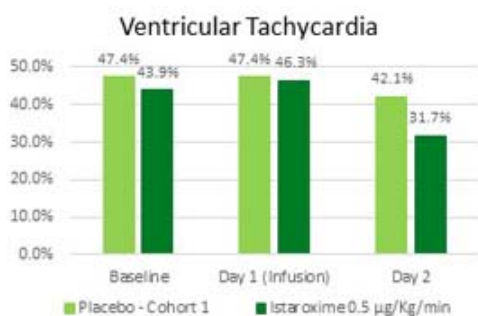
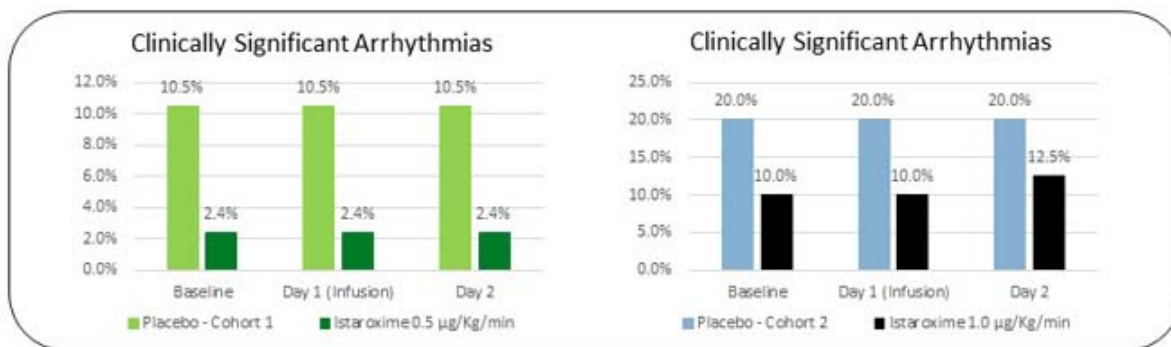


Cardiac TnT (Myocardial Damage)

cTnT – 24 to 72 hours



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

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

Execute an additional study designed to complete Phase 2 and inform Phase 3

- 300 patients, 60 centers globally*



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



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

Istaroxime

Early Cardiogenic Shock

Additional potential indication in active clinical development





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 survivors¹
- Represents an approximate \$1.25B total market potential²

Early Cardiogenic Shock Treatment

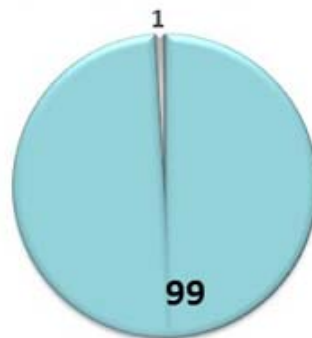
Istaroxime Potential Opportunity to Address Significant Unmet Need

- **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 Research¹

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

Clinical Cardiologists Treating



■ Highly Needed ■ Low Need

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

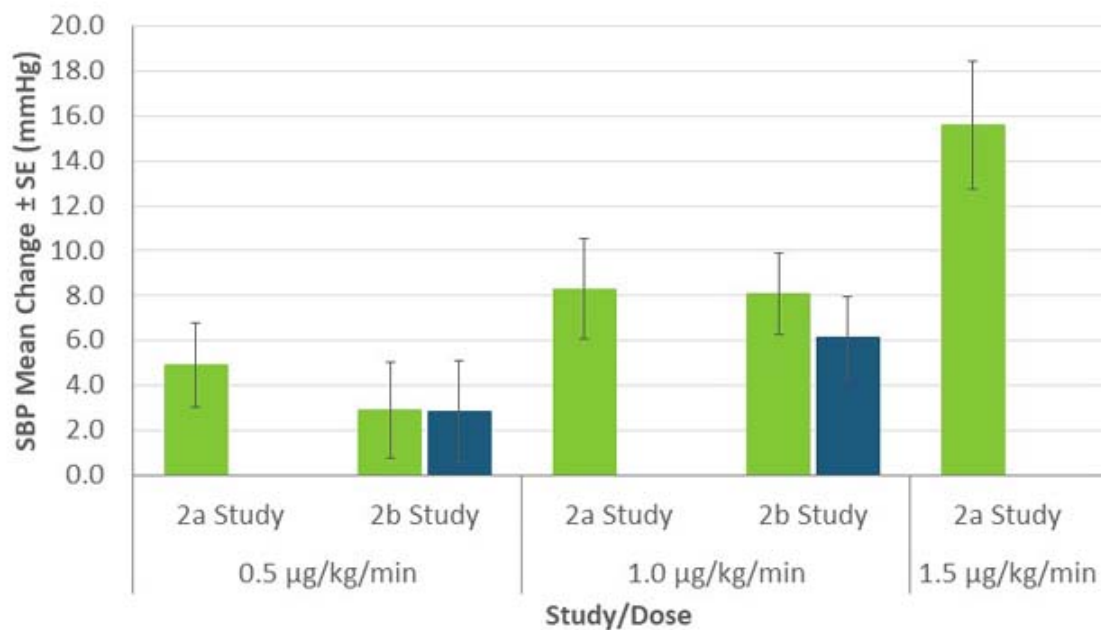
Potential for a complementary program that may have a scale which is faster and less expensive than the fundamental, larger AHF development program



- 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

■ 6 Hours ■ 24 Hours

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 ≥ 90 mmHg)
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

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

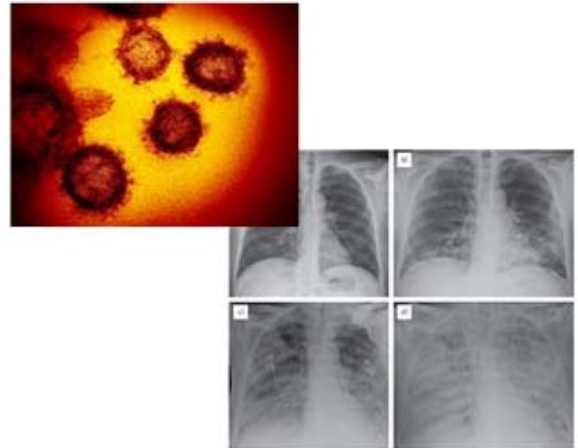
Potential to Create Value

- 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

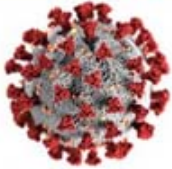
Lyo Lucinactant

Synthetic KL4 Surfactant

Lung Injury in COVID-19 Patients



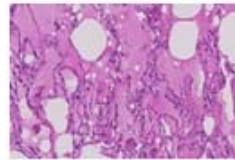
COVID-19 and ARDS Have Significant Negative Impact on Surfactant-Related Lung Function



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

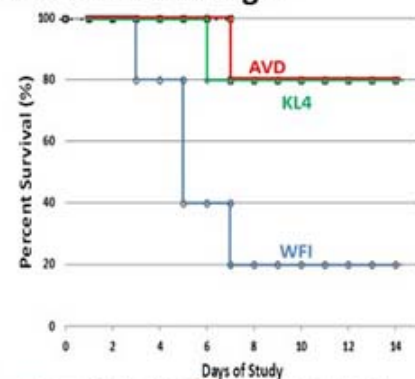


Surfactant is necessary for lungs to stay inflated and for proper gas exchange; Type 2 cell damage results in impaired surfactant production



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



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

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

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

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 sites in US and 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)

Results

- ✓ Generally safe and well tolerated and could be safely administered to critically ill, mechanically ventilated patients with severe COVID-19 ARDS
- ✓ Oxygenation and other physiological outcomes were generally stable or improved
- ✓ The results in this study support the feasibility of this approach to develop a potential treatment for critically ill patients with ARDS due to COVID-19 and other causes

AEROSURF

*Synthetic KL4 Surfactant with
Proprietary Aerosol Delivery System*




Respiratory Distress Syndrome (RDS)



Respiratory Distress Syndrome (RDS)

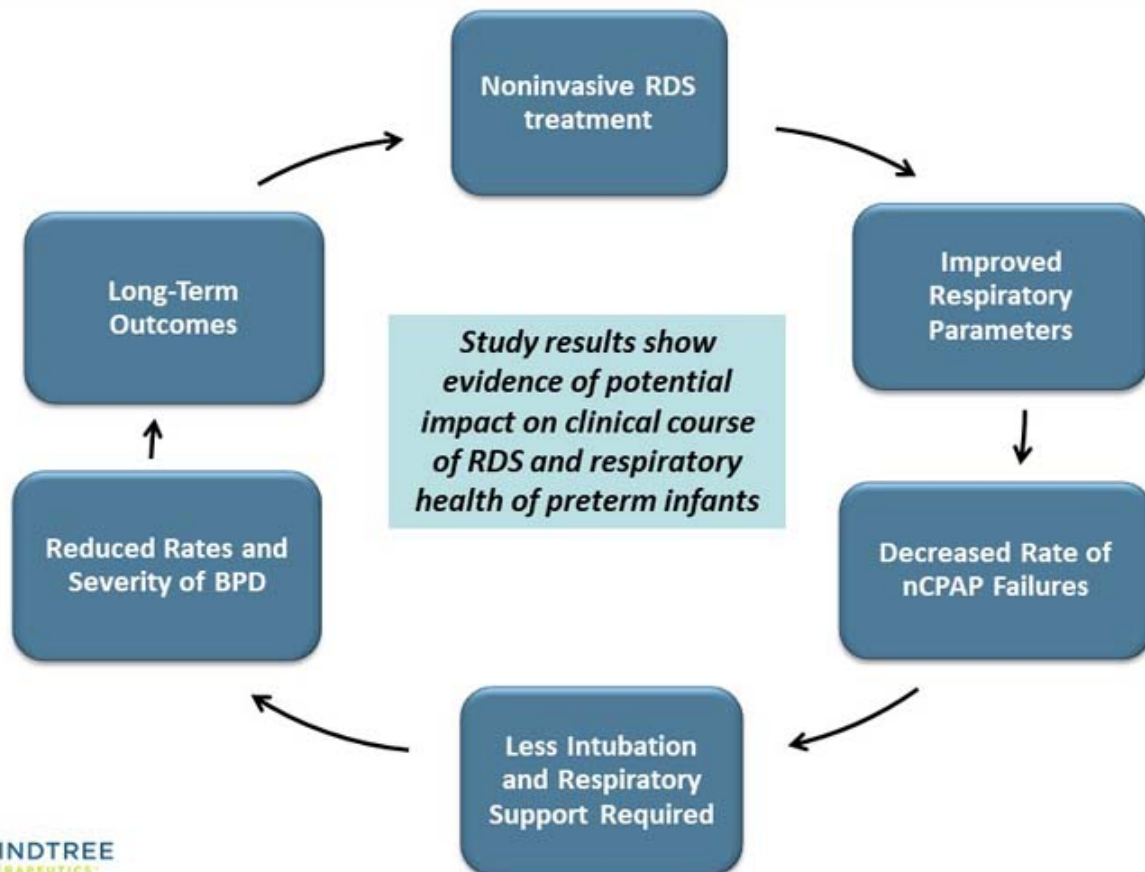
Current Treatment Pathways

- 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	<ul style="list-style-type: none"> ▪ Proprietary Synthetic KL4 surfactant⁽¹⁾; <ul style="list-style-type: none"> – Structurally similar to human lung surfactant 	<ul style="list-style-type: none"> ▪ Animal derived 	<ul style="list-style-type: none"> ▪ None
Method of Delivery	<ul style="list-style-type: none"> ▪ Proprietary aerosol delivery system (ADS) with nCPAP 	<ul style="list-style-type: none"> ▪ Intubation usually in combination with mechanical ventilation 	<ul style="list-style-type: none"> ▪ Nasal prongs
The AEROSURF Difference	<ul style="list-style-type: none"> ▪ 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) 	<ul style="list-style-type: none"> ▪ Timely therapy, but exposure to known significant complications associated with invasive intubation 	<ul style="list-style-type: none"> ▪ Avoid exposure to significant complications ▪ Foregoing surfactant treatment results in notable nCPAP failure rate and intubations

AEROSURF® – Potential to Impact the Clinical Course of RDS

Building Evidence From Nearly 400 Patients Studied



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

Financial Summary & Capitalization as of December 31, 2021

- Cash & Equivalents of ~\$22.3 million

Securities	Common Equivalents as of March 30, 2022
Common Stock	28,469,274
Options (WAEP \$8.04)	4,173,033
Restricted Stock Units	554,000
Warrants (WAEP \$9.43)	16,628,802
Fully Diluted Equivalents	49,825,109



- ✓ **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!”



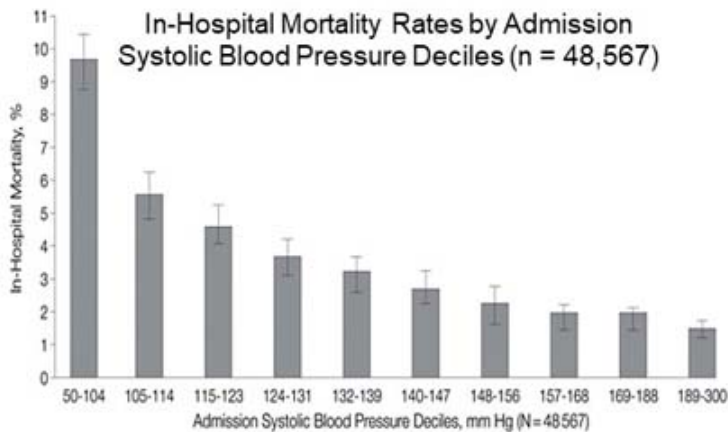
Appendix



Acute Heart Failure

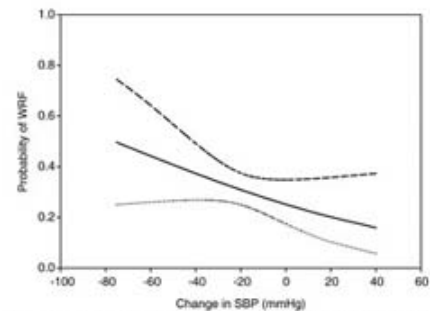
Significant Healthcare Issue with Significant Unmet Clinical Need

- **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 SBP¹
 - There is a direct relationship between early drop in SBP and worsening renal function in acute heart failure²



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



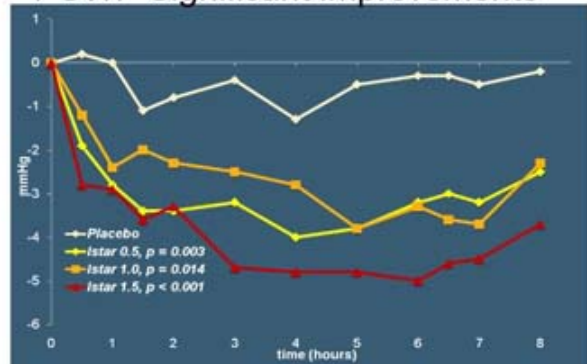
- 1) ADHERE Registry, n=48,567; JAMA 2006
- 2) European Journal of Heart Failure; Voors, PRE-RELAX AHF Study; 2011; 13

Istaroxime Phase 2a (HORIZON-HF) Study

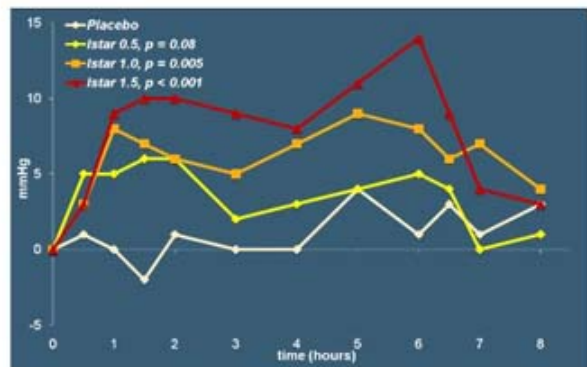
- Multicenter, double blind, placebo-controlled, doses 6-hour infusion of istaroxime 0.5, 1.0, 1.5 $\mu\text{g}/\text{kg}/\text{min}$, conducted in the EU
- Hospitalized with AHF, with criteria including:
 - LVEF $\leq 35\%$
 - SBP 90-150 mmHg
- N=120 (30/group)
- Significant improvement in PCWP, SBP,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

Primary Endpoint:

PCWP Significant Improvements



Dose-dependent Increase in SBP



Istaroxime 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

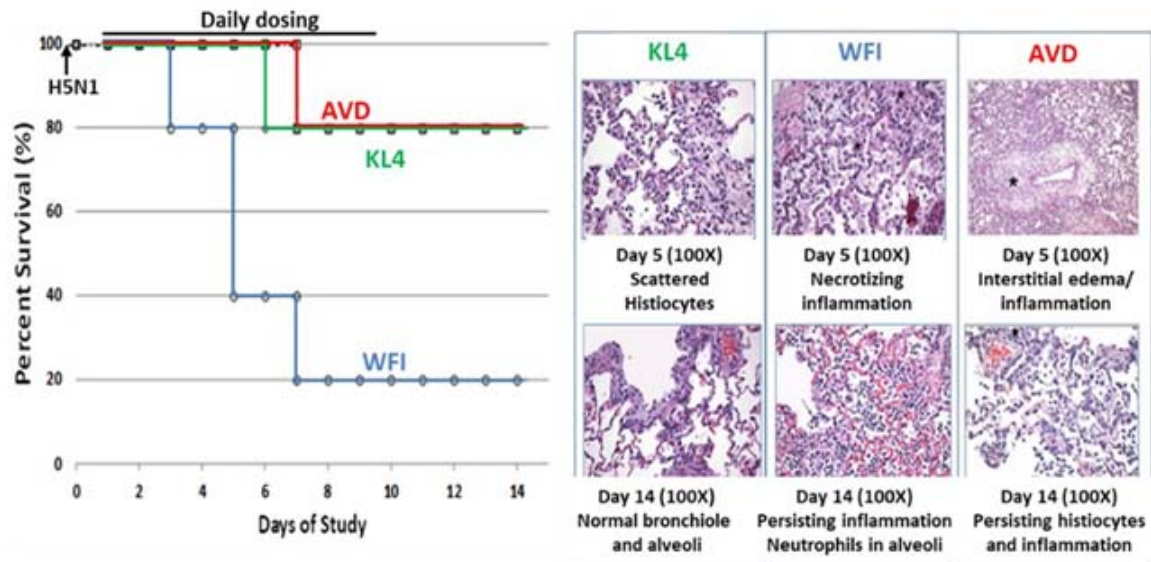
††Most common - arrhythmia, atrial fibrillation, cardiac failure, ventricular tachycardia

‡ 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

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)

- Animal-derived surfactant
- Delivered via intubation, usually in combination with mechanical ventilation

VS.

nCPAP support until endogenous surfactant production

- 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

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**



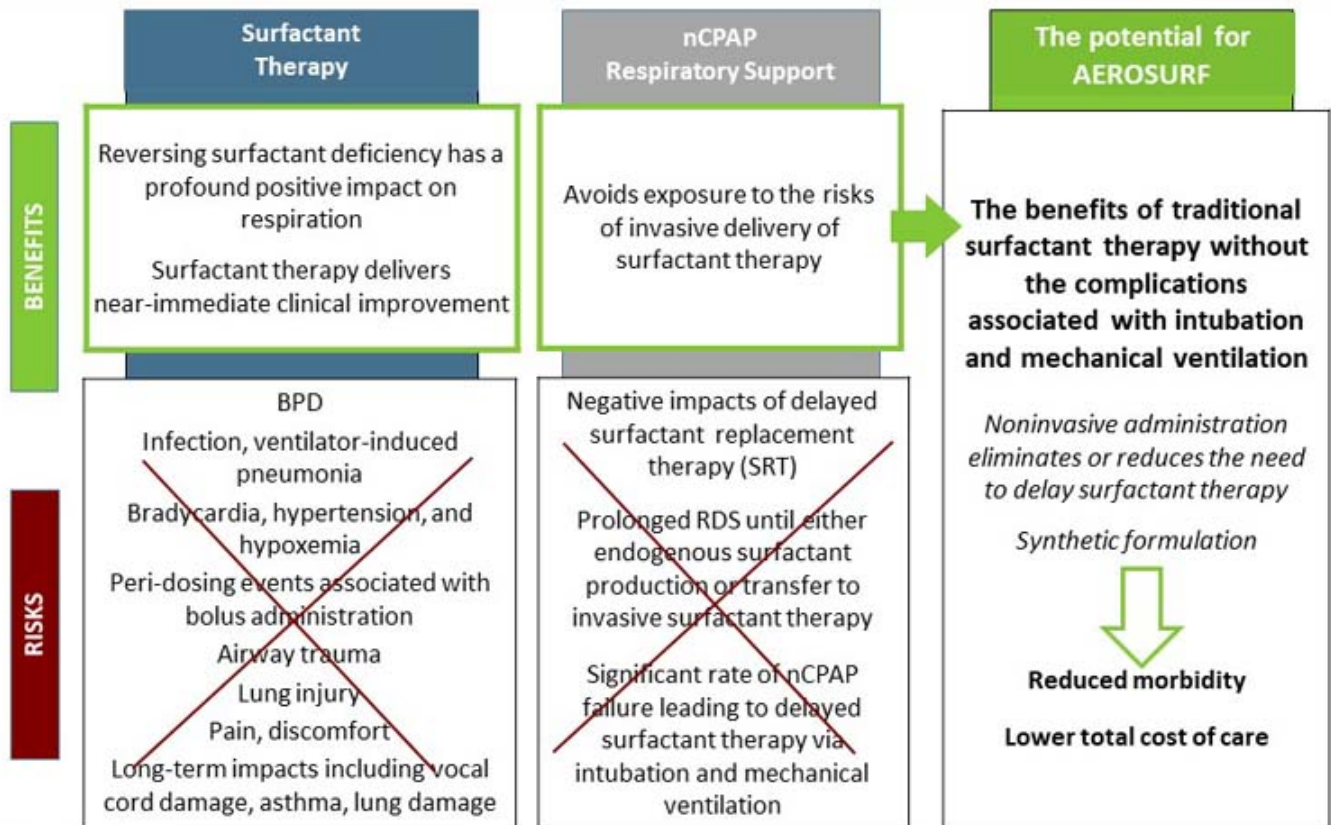
Utilizing pressure and heated
capillary has demonstrated
ability to **aerosolize KL4 surfactant**

**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

Transformative Potential of AEROSURF®



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