# 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): November 10, 2021**

# 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 2.02 Results of Operations and Financial Condition**

On November 10, 2021, Windtree Therapeutics, Inc. (the "***Company***") issued a press release announcing its financial results for the quarter ended September 30, 2021. A copy of the press release is furnished as Exhibit 99.1 to this Current Report on Form 8-K and is incorporated herein by reference.

The information contained in this Item 2.02 (including Exhibit 99.1) is being furnished and shall not be deemed "filed" for purposes of Section 18 of the Securities Exchange Act of 1934, as amended (the "***Exchange Act***"), or otherwise subject to the liabilities of that section and shall not be deemed to be incorporated by reference in any filing under the Securities Act of 1933, as amended, or the Exchange Act, except as shall be expressly set forth by specific reference in such filing.

**Item 8.01 Other Events**

On November 10, 2021, 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**

| Exhibit No. | Document |
|---|---|
| 99.1 | Press Release of Windtree Therapeutics, Inc., dated November 10, 2021, announcing financial results for the quarter ended September 30, 2021, furnished herewith. |
| 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: November 10, 2021

**Exhibit 99.1**

# Windtree Therapeutics Reports Third Quarter 2021 Financial Results and Provides Key Business Updates

**WARRINGTON, PA** – **November 10, 2021** – 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 third quarter ended September 30, 2021 and provided key business updates.

"I am very pleased to report on another productive quarter for Windtree. We continue to make progress with istaroxime, our lead clinical product candidate, and are focused on completing our phase 2 global study for the treatment of early cardiogenic shock, where we plan to announce topline data in Q1 2022. The need for new critical care cardiovascular therapies was clearly articulated during our KOL event held in October as well as in market research, and we believe istaroxime has the potential to be a meaningful new therapeutic innovation. The team is also busy preparing for the next study in our foundational program, acute heart failure with istaroxime. Concurrently, we are advancing an open-label phase 2 study of lucinactant (KL4) in patients with COVID-19 associated acute respiratory distress syndrome (ARDS) and anticipate topline data from this study in Q1 2022," said Craig Fraser, President and Chief Executive Officer of Windtree. "Our business development group continues to be very active as we explore opportunities and engage with potential partners. Our balance sheet provides sufficient support of our upcoming clinical and regulatory milestones as well as company operations through 2022."

**Key Business and Financial Updates**

- Hosted Key Opinion Leader (KOL) webinar on istaroxime for the treatment of acute heart failure and the upcoming data in early cardiogenic shock, featuring a presentation by John Teerlink, M.D., University of California, San Francisco. Dr. Teerlink presented the current treatment landscape, highlighted the unmet medical need in treating patients with acute heart failure, and discussed the potential role for istaroxime based on clinical data he presented. Management followed with a presentation covering the clinical development program for istaroxime in early cardiogenic shock, which is currently in a phase 2 global study with data expected in the first quarter of 2022.

- Continued executing the Company's lead program for istaroxime in the treatment of patients in early cardiogenic shock due to heart failure. These patients are characterized by very low blood pressure and risk for hypo-perfusion to critical organs. The ongoing phase 2 global study is designed to build upon data which showed istaroxime improved cardiac function and dose-related increases in systolic blood pressure in acute heart failure patients.

- Shared results from a U.S. physician survey and market research estimating that the worldwide total market value of cardiogenic shock is $1.25 billion. In the survey results, 99 out of 100 U.S.-based cardiologists responded that there was high need for pharmacologic (drug) treatment for early cardiogenic shock patients. Additionally, 84% of the cardiologists responded that for early cardiogenic shock patients they would be "likely to extremely likely" to use a drug with the observed characteristics of istaroxime.

- Announced that the United States Patent and Trademark Office (USPTO) issued a Notice of Allowance of new patent claims for istaroxime administration. A notice of allowance is issued by the USPTO to indicate that the application has passed examination. When the new patent is issued by the USPTO, it will provide new intellectual property protection for istaroxime until late 2039.

- Presented a corporate overview at the Oppenheimer Fall Healthcare Life Sciences and MedTech Summit.

**Select Financial Results for the Third Quarter ended September 30, 2021**

For the third quarter ended September 30, 2021, the Company reported an operating loss of $8.1 million, compared to an operating loss of $8.7 million in the third quarter of 2020.

Research and development expenses were $4.7 million for the third quarter of 2021, compared to $3.9 million for the third quarter of 2020. The increase in research and development expenses is primarily due to an increase of $0.6 million for the clinical activity and development of istaroxime in early cardiogenic shock and acute heart failure.

General and administrative expenses for the third quarter of 2021 were $3.5 million, compared to $4.8 million for the third quarter of 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 $0.6 million in professional fees.

The Company reported a net loss of $8.2 million ($0.31 per basic share) on 26.7 million weighted-average common shares outstanding for the quarter ended September 30, 2021, compared to a net loss of $9.0 million ($0.54 per basic share) on 16.6 million weighted average common shares outstanding for the comparable period in 2020.

As of September 30, 2021, the Company reported cash and cash equivalents of $24.5 million. During October 2021, the Company raised an additional $3.2 million through its At-The-Market (ATM) program. The Company's cash and cash equivalents as of September 30, 2021 and the additional funding from the ATM program are expected to be sufficient to fund operations through at least the next twelve months.

Readers are referred to, and encouraged to read in its entirety, the Company's Quarterly Report on Form 10-Q for the quarter ended September 30, 2021, which will be filed with the Securities and Exchange Commission on November 10, 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. 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.

For more information, please visit the Company's website at www.windtreetx.com.

**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 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, INC. AND SUBSIDIARIES**
**Condensed Consolidated Balance Sheets**

*(in thousands, except share and per share data)*

| | September 30, 2021 | December 31, 2020 |
|---|---|---|
| | Unaudited | |
| **ASSETS** | | |
| Current Assets: | | |
| Cash and cash equivalents | $ 24,541 | $ 16,930 |
| Prepaid expenses and other current assets | 1,826 | 1,188 |
| Total current assets | 26,367 | 18,118 |
| Property and equipment, net | 890 | 924 |
| Restricted cash | 154 | 154 |
| Operating lease right-of-use assets | 2,412 | 917 |
| Intangible assets | 39,320 | 77,090 |
| Goodwill | 15,682 | 15,682 |
| Total assets | $ 84,825 | $ 112,885 |
| **LIABILITIES & STOCKHOLDERS' EQUITY** | | |
| Current Liabilities: | | |
| Accounts payable | $ 582 | $ 1,161 |
| Accrued expenses | 3,549 | 3,813 |
| Operating lease liabilities - current portion | 278 | 805 |
| Loans payable - current portion | 734 | 352 |
| Total current liabilities | 5,143 | 6,131 |
| Operating lease liabilities - non-current portion | 2,196 | 201 |
| Loans payable - non-current portion | - | 2,423 |
| Restructured debt liability - contingent milestone payments | 15,000 | 15,000 |
| Other liabilities | 3,600 | 2,800 |
| Deferred tax liabilities | 8,707 | 16,778 |
| Total liabilities | 34,646 | 43,333 |
| Stockholders' Equity: | | |
| Preferred stock, $0.001 par value; 5,000,000 shares authorized; 0 shares issued and outstanding at September 30, 2021 and December 31, 2020 | - | - |
| Common stock, $0.001 par value; 120,000,000 shares authorized at September 30, 2021 and December 31, 2020; 26,704,480 and 16,921,506 shares issued at September 30, 2021 and December 31, 2020, respectively; 26,704,456 and 16,921,482 shares outstanding at September 30, 2021 and December 31, 2020, respectively | 27 | 17 |
| Additional paid-in capital | 825,457 | 790,277 |
| Accumulated deficit | (772,251) | (717,688) |
| Treasury stock (at cost); 24 shares | (3,054) | (3,054) |
| Total stockholders' equity | 50,179 | 69,552 |
| Total liabilities & stockholders' equity | $ 84,825 | $ 112,885 |

**WINDTREE THERAPEUTICS, INC. AND SUBSIDIARIES**
**Condensed Consolidated Statements of Operations**
(Unaudited)

*(in thousands, except per share data)*

| | Three Months Ended September 30, | | Nine Months Ended September 30, | |
|---|---|---|---|---|
| | 2021 | 2020 | 2021 | 2020 |
| Expenses: | | | | |
| Research and development | $ 4,680 | $ 3,882 | $ 13,311 | $ 11,838 |
| General and administrative | 3,467 | 4,823 | 11,507 | 11,518 |
| Loss on impairment of intangible assets | - | - | 37,770 | - |
| Total operating expenses | 8,147 | 8,705 | 62,588 | 23,356 |
| Operating loss | (8,147) | (8,705) | (62,588) | (23,356) |
| | | | | |
| Other income (expense): | | | | |
| Interest income | 1 | 21 | 90 | 115 |
| Interest expense | (14) | (46) | (101) | (121) |
| Other (expense), net | (53) | (290) | (296) | (1,750) |
| Total other (expense), net | (66) | (315) | (307) | (1,756) |
| | | | | |
| Loss before income taxes | (8,213) | (9,020) | (62,895) | (25,112) |
| Deferred income tax benefit | - | - | 8,332 | - |
| Net loss | $ (8,213) | $ (9,020) | $ (54,563) | $ (25,112) |
| | | | | |
| Net loss per common share | | | | |
| Basic and diluted | $ (0.31) | $ (0.54) | $ (2.31) | $ (1.65) |
| | | | | |
| Weighted average number of common shares outstanding | | | | |
| Basic and diluted | 26,704 | 16,579 | 23,616 | 15,228 |

# Windtree Therapeutics

## Company Overview

November 2021

(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 and medical device company with **four 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**:
  - Two clinical programs received Fast Track and Orphan Drug Designations; one program with potential for Breakthrough Designation

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

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

# Windtree Therapeutics Pipeline

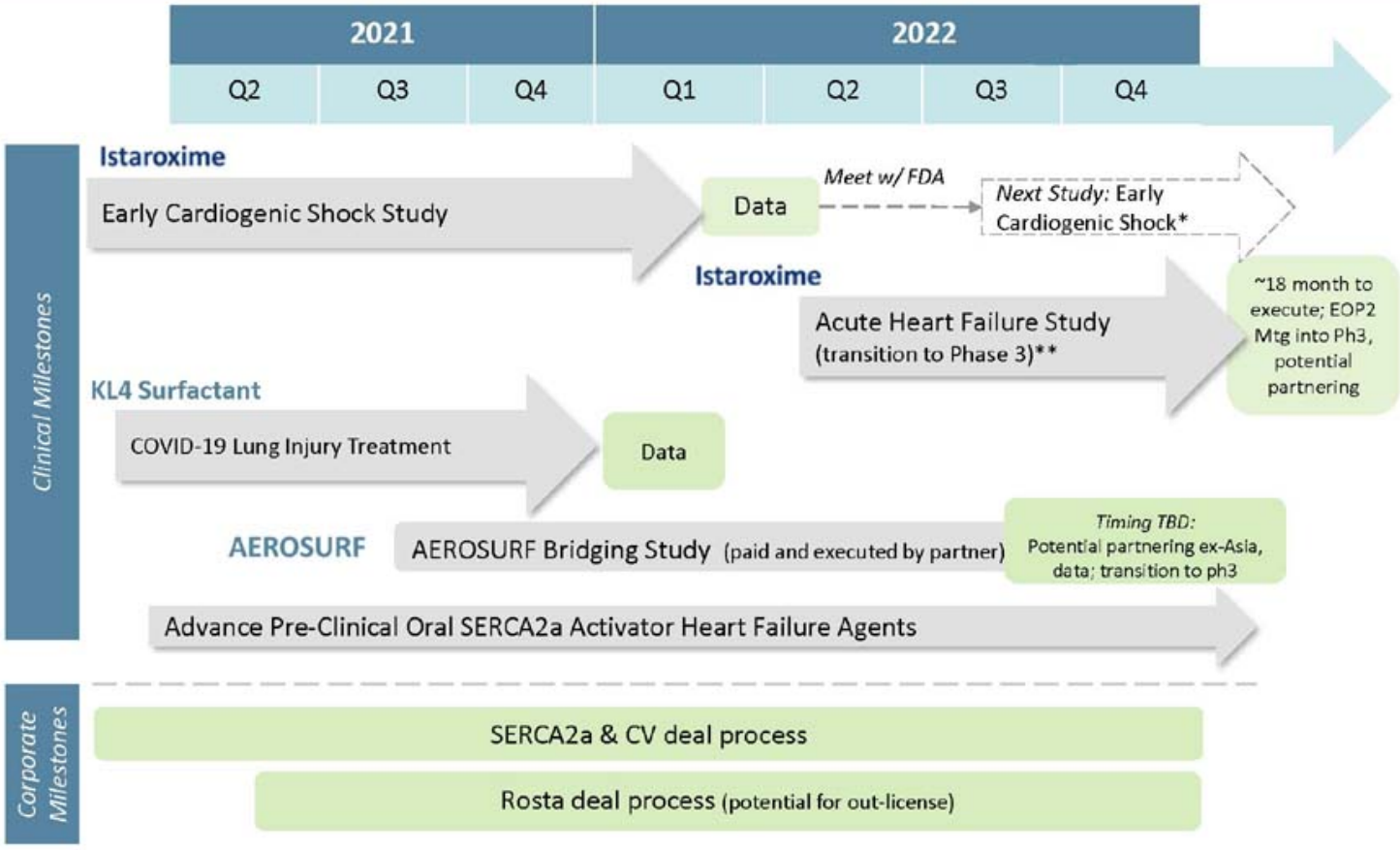
| | Lead Products | Pre- | Phase I | Phase II | Phase III | Next Milestone |
|---|---|---|---|---|---|---|
| *FDA Fast Track Designation* | **Istaroxime** (Acute Heart Failure) | | | Phase 2b | | ▪ Study start up ongoing for second Phase 2b clinical trial in ~300 patients targeted to start once clinical trial operations are fully funded |
| *Potential for Breakthrough designation* | **Istaroxime** (Early Cardiogenic Shock) | | | Phase 2 | | ▪ Ongoing global clinical study in early cardiogenic shock; Data currently expected Q1 2022* |
| | **Oral SERCA2a Activators** (Chronic HF; potentially HFpEF) | | | Preclinical | | ▪ Chronic and Acute Heart Failure<br>▪ Target for collaboration/partnership |
| *FDA, EMA Orphan Drug for RDS* | **KL4 Surfactant – COVID 19** (COVID 19 Pilot; Open-Label) | | | Phase 2 | | ▪ IND Accepted; Initiated trial Q1 2021; Data currently expected Q1 2022* |
| *FDA Fast Track Designation, Orphan Drug* | **AEROSURF** (KL4 surfactant Drug/Device Tx for Preterm Infants with RDS) | | | Phase 2b | | ▪ Bridge study with our ADS (Aerosol Delivery System) to be funded and executed by licensee |
| | **Rostafuroxin** (Genetically Associated HTN) | | | Phase 2b | | ▪ Out-licensing opportunity |

WINDTREE THERAPEUTICS

*Potential for continued COVID-19 impact to trial conduct and timelines

# Strategy for Value Creation
## *Planned Milestones*

*Potential for continued COVID-19 impact to trial conduct and timelines*




WINDTREE THERAPEUTICS

*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

WINDTREE THERAPEUTICS

# 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

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**

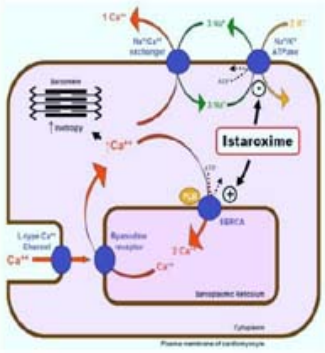
Dual Mechanism of Action

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)

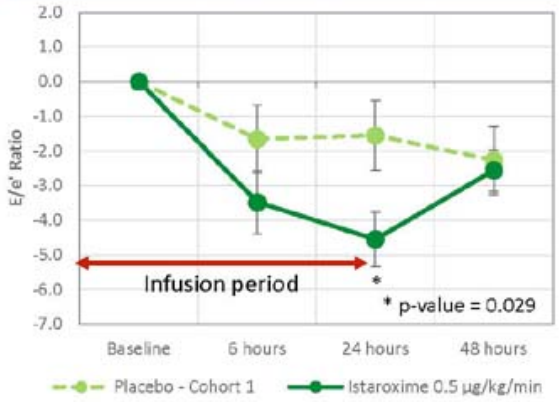
**Positive Phase 2 trial results demonstrated improved cardiac function without unwanted side effects of existing therapies**

WINDTREE THERAPEUTICS

# Primary Endpoint Achieved

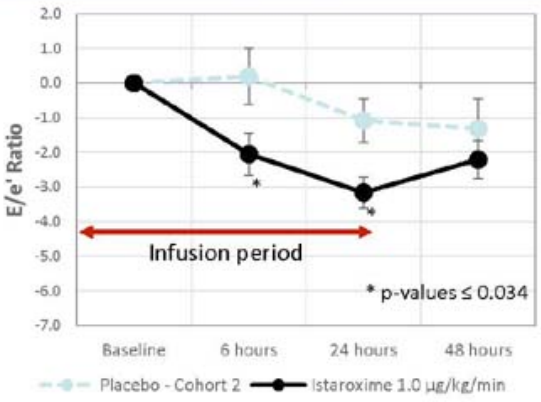
*Significant Changes in E/e' Ratio[1] and Stroke Volume*

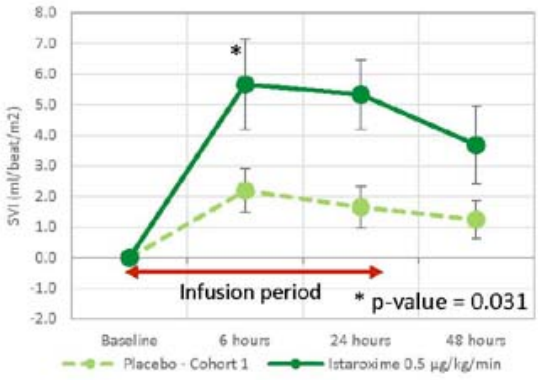
istaroxime 0.5 µg/kg/min vs. placebo



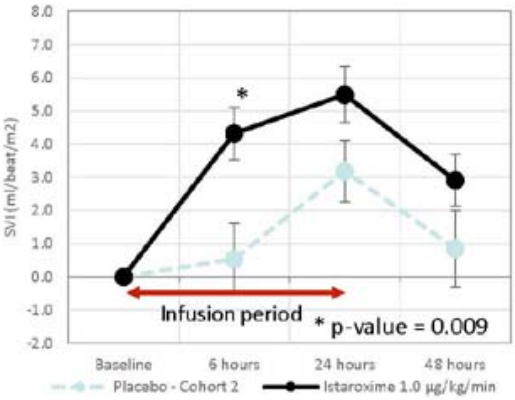

E/e'

istaroxime 1.0 µg/kg/min vs. placebo




**Stroke Volume**

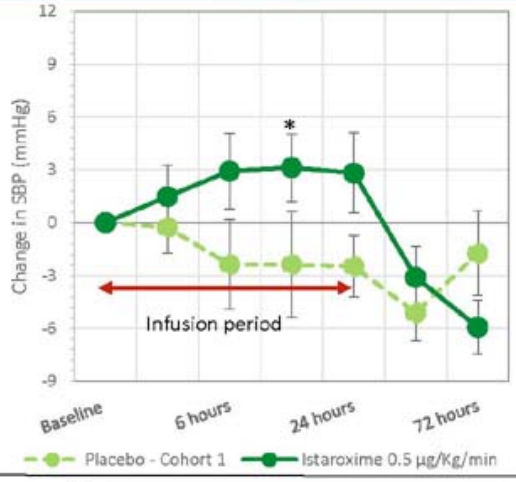



WINDTREE THERAPEUTICS

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

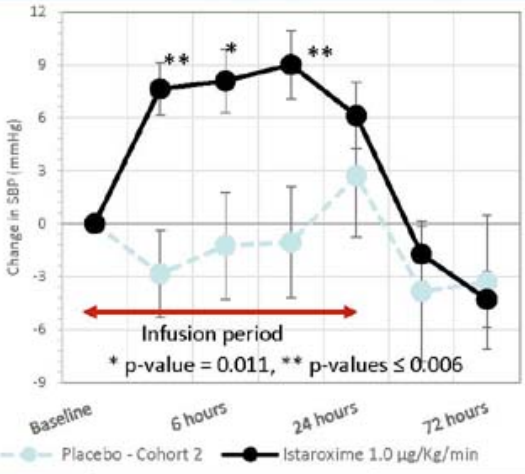
# Systolic Blood Pressure Increased During Treatment and Renal Function Tended to Improve

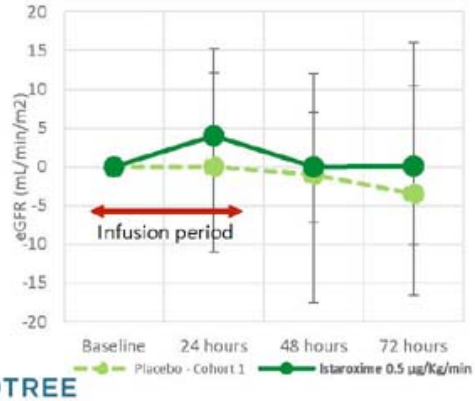
istaroxime 0.5 µg/kg/min vs. placebo



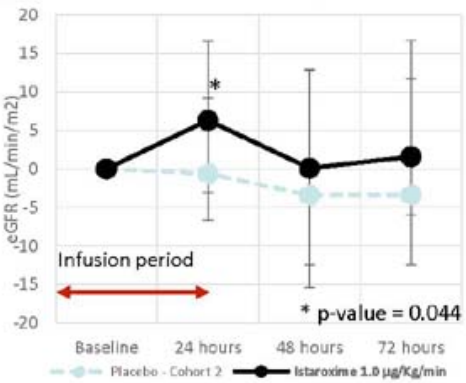

**Systolic Blood Pressure (SBP)**

istaroxime 1.0 µg/kg/min vs. placebo




**GFR (Renal Function)**

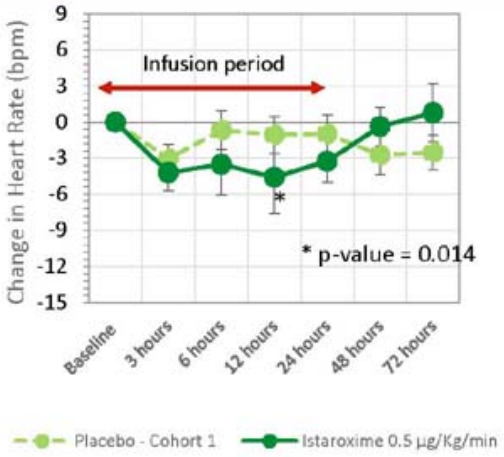



WINDTREE THERAPEUTICS

Data shown as means and standard errors

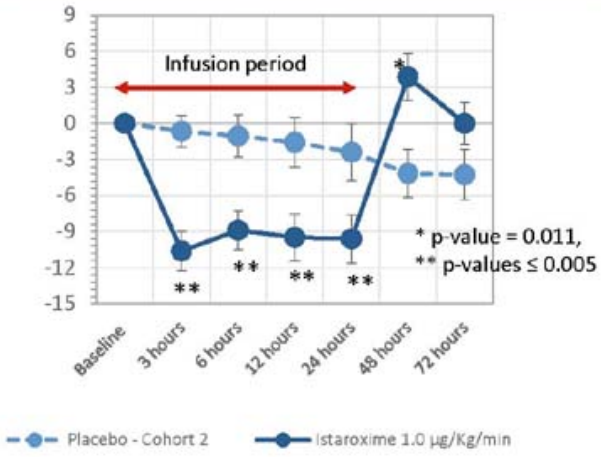
# Heart Rate Decreased and No Increases in Cardiac Troponins

istaroxime 0.5 µg/kg/min vs. placebo

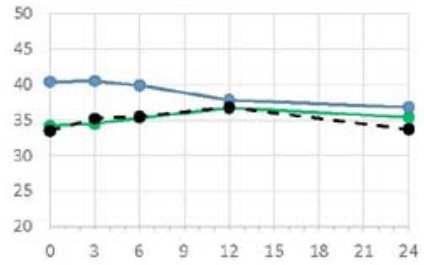



**Heart Rate**

istaroxime 1.0 µg/kg/min vs. placebo

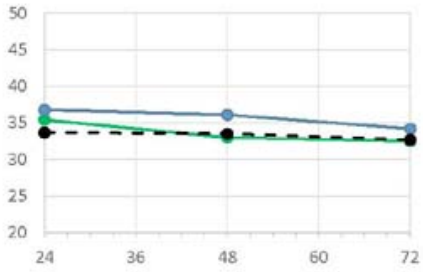



**cTnT – 0 to 24 hours**




**Cardiac TnT (Myocardial Damage)**

**cTnT – 24 to 72 hours**

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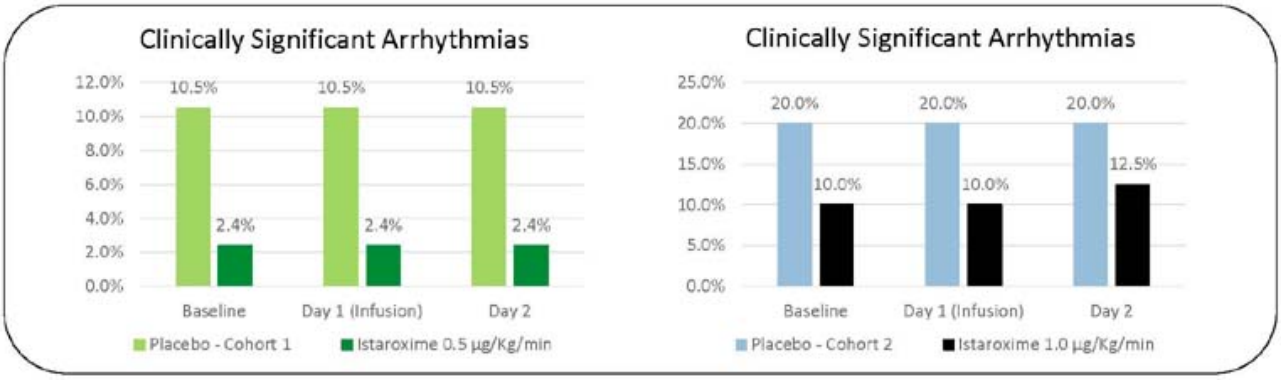
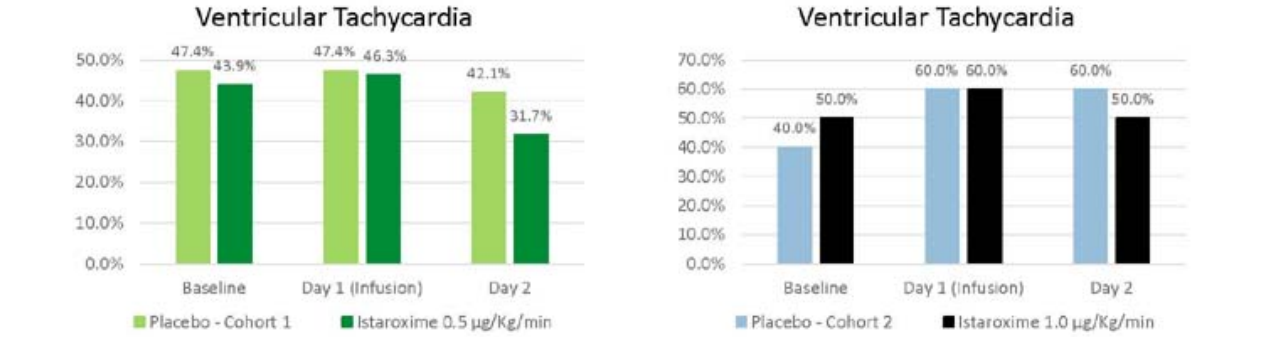
# Favorable Profile Observed with 24-hour Holter Monitoring




WINDTREE THERAPEUTICS

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

# 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**

**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

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]



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

# Early Cardiogenic Shock Treatment

*Istaroxime Potential Opportunity to Address Significant Unmet Need*

- **No satisfactory pharmacological intervention to reverse the conditions**
  - Available therapies have unwanted side effects such as risk for arrhythmias, decreasing blood pressure, renal dysfunction and even increases in mortality that limit their usefulness and position them as "rescue medicines" for severe cases
- **A therapy that can be used earlier to rapidly improve blood pressure and cardiac function without unwanted side effects is needed**

## Market Research[1]

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

**Clinical Cardiologists Treaters**


84% of the cardiologists responded they would be likely to extremely likely to use istaroxime for early cardiogenic shock patients

Majority responded they would position utilization before use of other existing classes of therapies such as inotropes and vasopressors

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

# Early Cardiogenic Shock Treatment

*Istaroxime Potential Opportunity for Accelerated Pathway*

**FDA Regulatory Commentary 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]

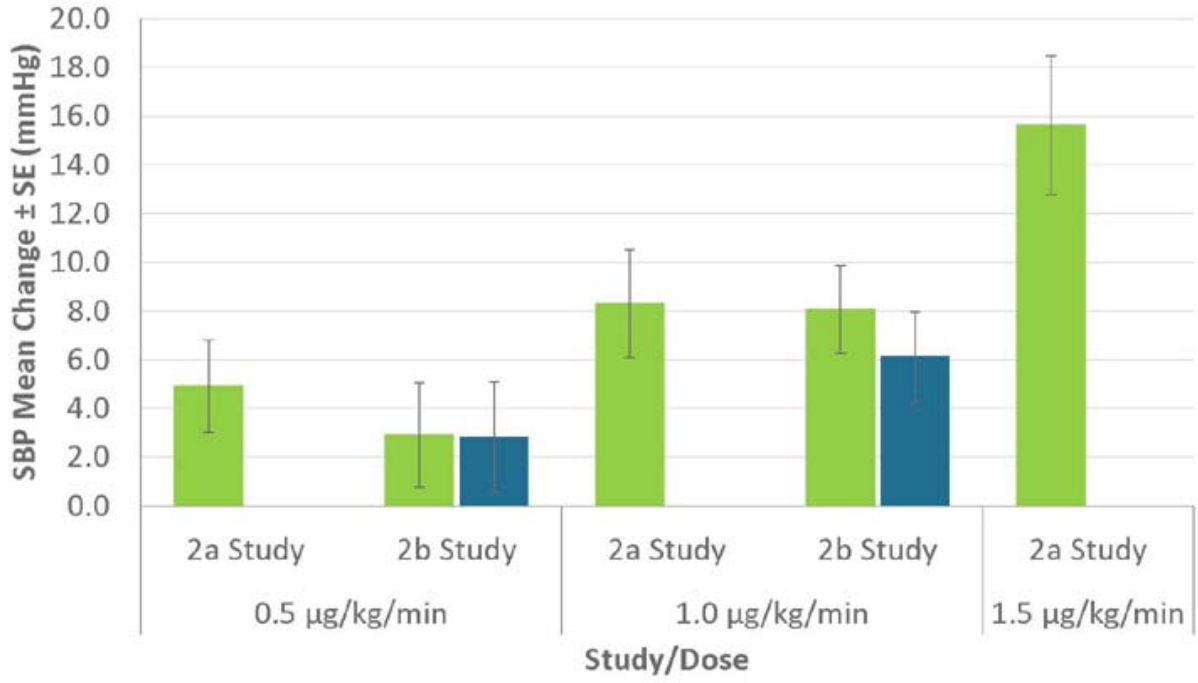
Precedent indicates potential accelerated regulatory pathway and review opportunities

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*

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# Istaroxime
*Early Cardiogenic Shock Study*

## Ongoing 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:*** *Data expected in Q1 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

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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**

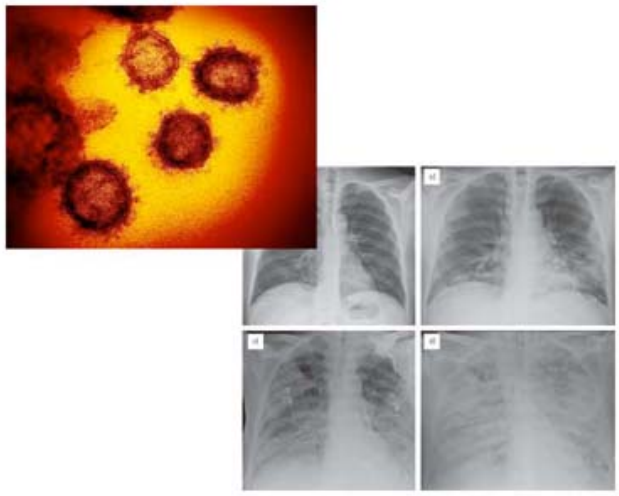
# Summary
*Potential to Create Value*

- 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 – 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
- Creating strong Phase 3 position: planned Istaroxime study will leverage unique profile in a target population that may most benefit from Istaroxime, dose longer and include measures that would inform the Phase 3
- Pathway to approval in Early Cardiogenic Shock may be faster: Istaroxime Early Cardiogenic Shock study with data expected in Q1 2022
  - Potential Opportunity for Breakthrough Designation
- Next generation, oral SERCA2a activators in early development create a multi-asset, chronic and acute heart failure platform

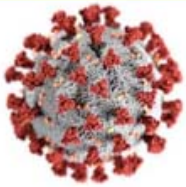
# Lyo Lucinactant

*Synthetic KL4 Surfactant*

## Lung Injury in COVID-19 Patients

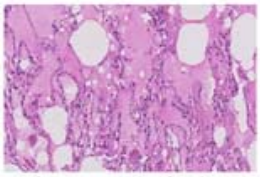


# COVID-19 and ARDS Have Significant Negative Impact on Surfactant-Related Lung Function



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

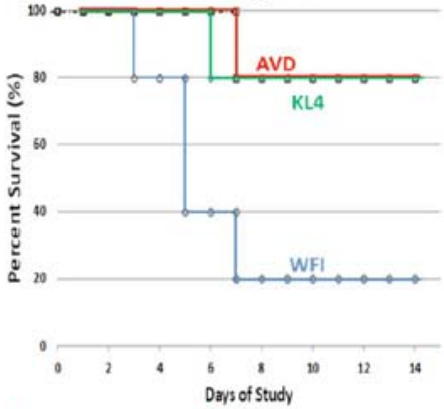
ACE2 is surface molecule on alveolar Type 2 lung cells – the source of surfactant



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

# Surfactant Administration in Severe COVID-19 Lung Injury May Have Potential to Provide Significant Benefits

- Synthetic KL4 surfactant may mitigate surfactant deficiency and resist widespread surfactant destruction that can occur as a result of COVID-19
- Synthetic KL4 surfactant removes any immunological concerns and has manufacturing scalability versus animal-derived surfactants

**Pre-clinical and clinical evidence shows surfactant replacement therapy has potential to:**

*Improve*

- Lung function
- Gas exchange and oxygenation
- Lung compliance

*Decrease*

- Inflammation in the lung which may decrease lung damage, facilitate recovery and decrease mechanical ventilation

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# 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, up to 20 patients from 4-5 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 administration
  - Physiologic response: Oxygenation Index (OI)
  - Lung compliance on the ventilator

**Data expected in Q1 2022**

***If study outcomes are favorable, plan to seek non-dilutive grant funding to expand the acute lung injury program***

# 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]:<br>– 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**<br>▪ **Improves respiratory parameters**<br>▪ **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**<br>▪ **Foregoing surfactant treatment results in notable nCPAP failure rate and intubations** |

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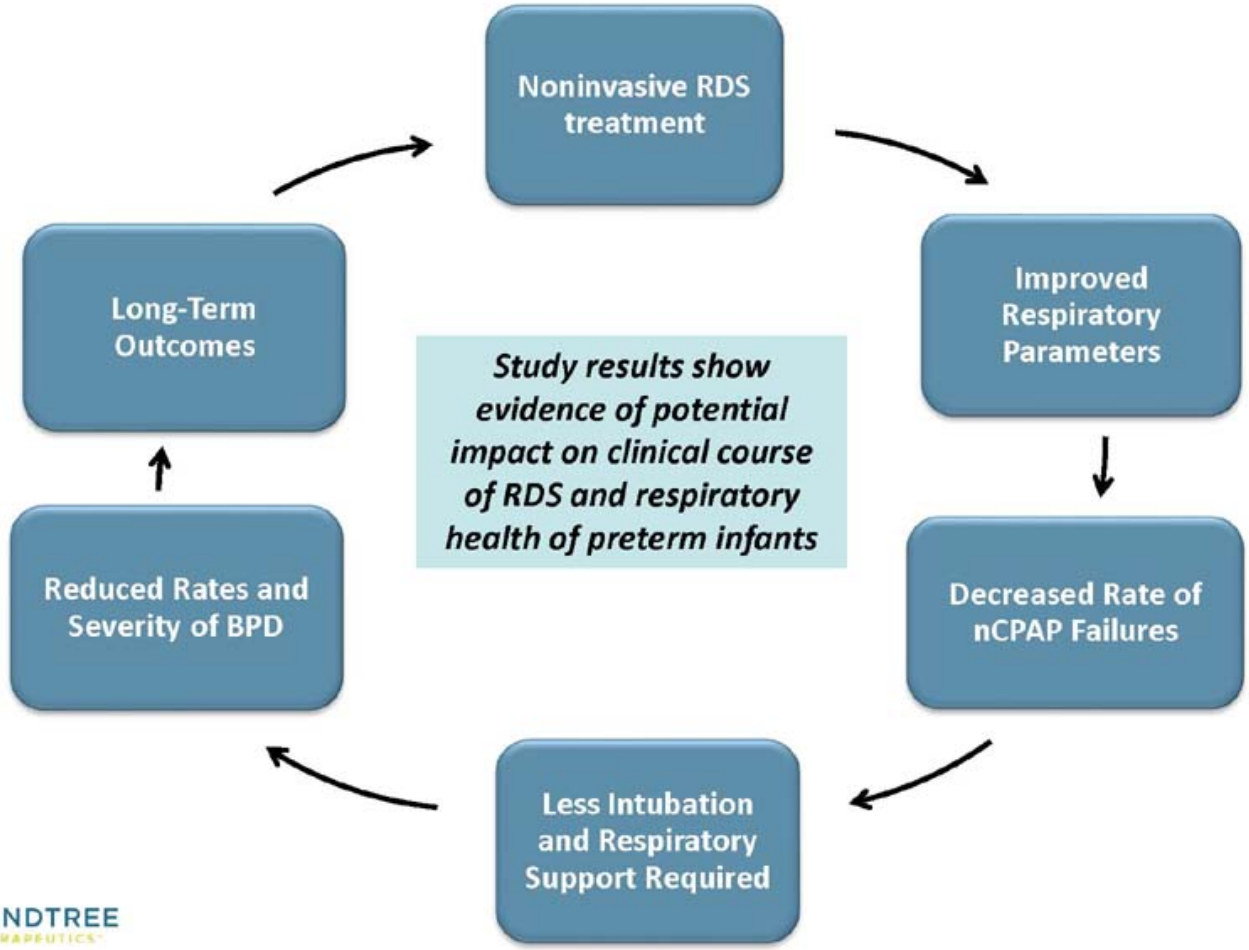
1) Liquid KL4 surfactant for RDS approved by the FDA. Lyophilized KL4 currently being developed for AEROSURF

# 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

- **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!"*

WINDTREE THERAPEUTICS

# Appendix

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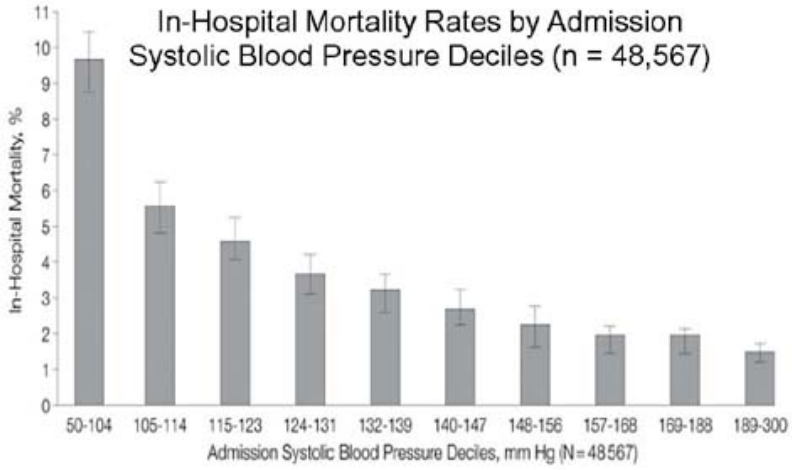
# Acute Heart Failure

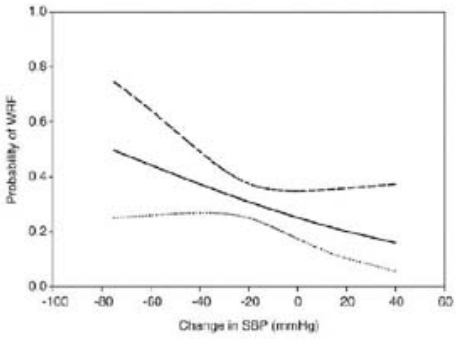
*Significant Healthcare Issue with Significant Unmet Clinical Need*

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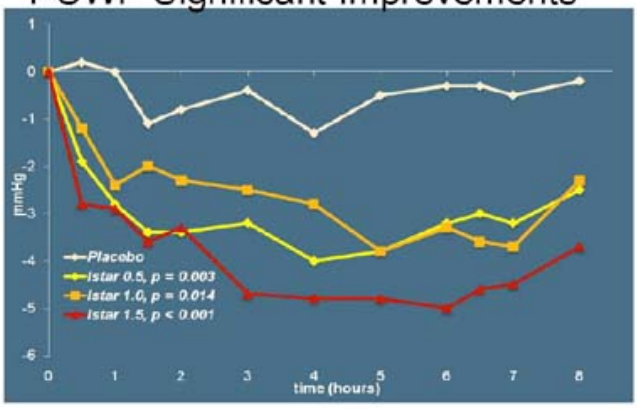
1) ADHERE Registry, n=48,567; JAMA 2006
2) European Journal of Heart Failure; Voors, PRE-RELAX AHF Study; 2011; 13

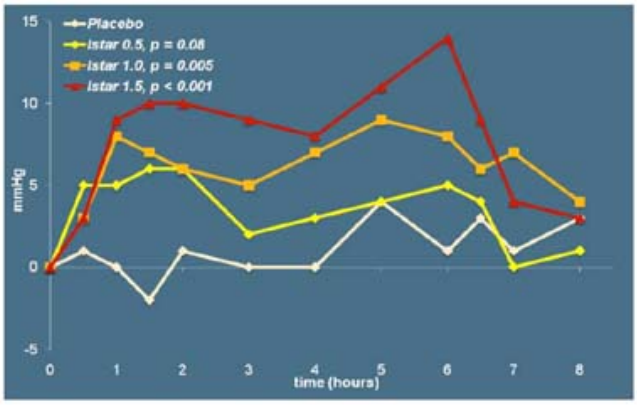
# Istaroxime Phase 2a (HORIZON-HF) Study

- 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

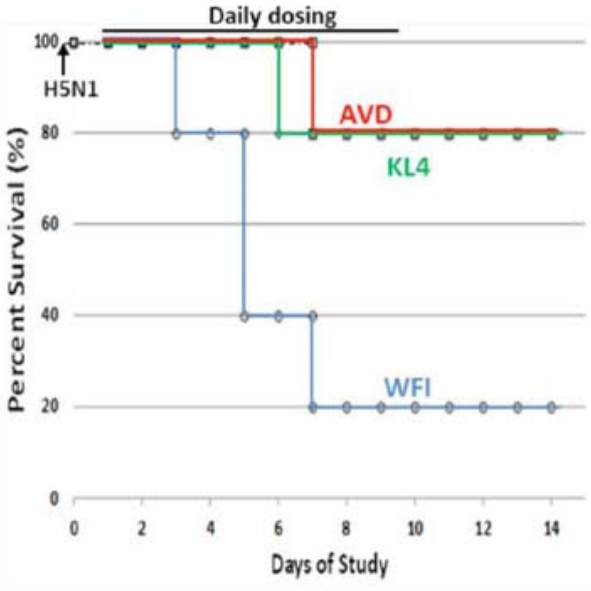
| Event | Pooled placebo (n=39) | istaroxime 0.5 mg/Kg/min (n=41) | istaroxime 1.0 mg/Kg/min (n=40) |
|---|---|---|---|
| **All adverse events** | 23 (59.0%) | 31 (75.6%) | 33 (82.5%) |
| **Adverse events leading to discontinuation** | 1 (2.6%) | - | 4 (10.0%) |
| **Serious adverse events** | 2 (5.1%) | 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%) |

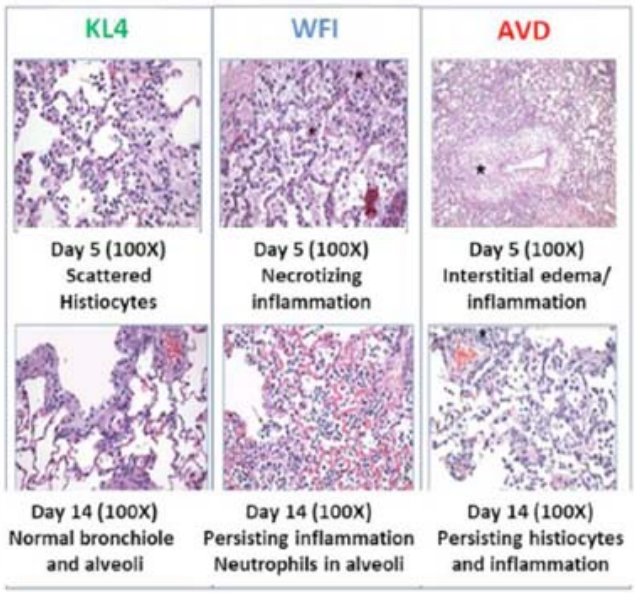
Note: data shown as n° patients (%) - patients can have more than one event during the 30-day follow up period
* Same patient who then died, and 1 additional death occurred at Day 31 (cardiac death) outside the 30 day window
† Adverse Drug Reactions are AEs related to study drug
††Most common - arrhythmia, 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<br>▪ 2,148 patients enrolled \| 1,028 treated<br>▪ 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<br>▪ 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<br>• Delivered via intubation, usually in combination with mechanical ventilation | | • Noninvasive nasal delivery of continuous positive airway pressure (nCPAP)<br>• 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

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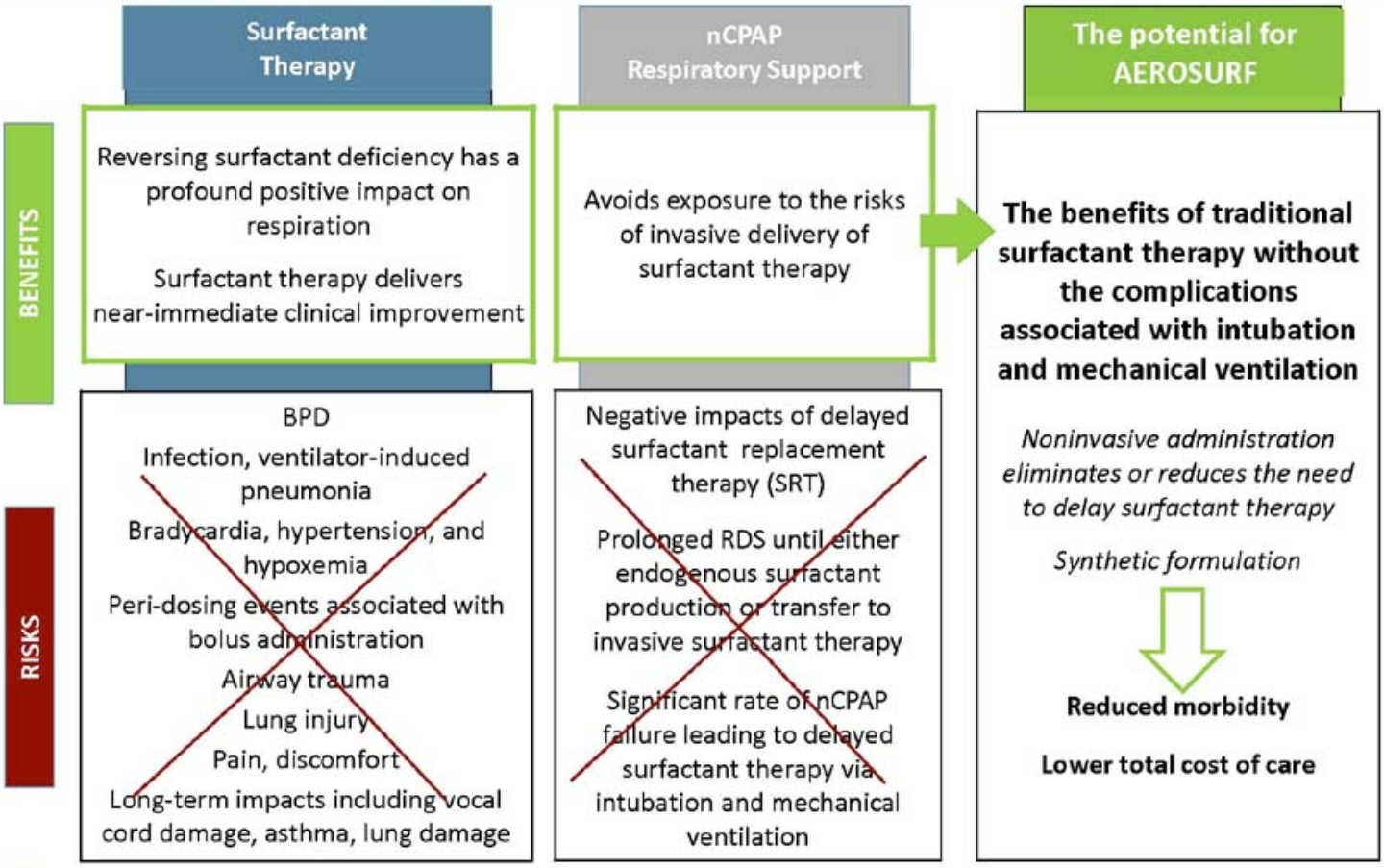
# Transformative Potential of AEROSURF®

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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