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M. Marin
312-265-9211
mmarin@zacks.com

scr.zacks.com
10 S. Riverside Plaza, Chicago, IL 60606

Windtree Therapeutics (WINT-NASDAQ)

WINT: Patient Enrollment in SEISMiC C Trial Starts, Patent Position Expands

Research Note

Enrolling SCAI Stage C participants in SEISMiC C trial, preparing for Phase 3 readiness

Pennsylvania-based Windtree Therapeutics, Inc. (NASDAQ: WINT), a biopharmaceutical company developing therapies for a range of cardiovascular and oncology treatments characterized by significant unmet need, implemented a number of measures recently to move lead asset istaroxime forward. The company's lead indication area is cardiogenic shock (which is a severe form of heart failure) with istaroxime. Windtree recently commenced enrollment in its SEISMiC C trial in SCAI Stage C cardiogenic shock (CS), after positive data from earlier SEISMiC A and B studies (see below) in SCAI Stage B cardiogenic shock trials that showed that istaroxime improved systolic blood pressure, cardiac function and renal function without an increased risk for cardiac arrhythmias. This profile differentiates istaroxime from currently used medications to treat shock.

To position istaroxime for Phase 3 readiness, WINT launched the small Phase 2 study in SCAI Stage C. SCAI Stage C cardiogenic shock is a more severely ill patient population than the participants previously treated in istaroxime studies. Specifically, SCAI Stage C patients have progressed to severe issues ensuing from cardiogenic shock and heart failure, including tissue and vital organ hypoperfusion (lack of blood flow and oxygen). These patient generally need inotropic or vasopressor drugs – which often have harmful side effects that WINT believes istaroxime can potentially avoid – to manage their care.

The company's SEISMiC C study is a global trial that includes participating centers in the U.S,. Europe and Latin America. It is a placebo-controlled, double-blinded study with istaroxime being added to current standard of care inotropes or vasopressors noted above. The effect of istaroxime in combination with these other therapies will be assessed for six hours. Based on the patient's condition, the study is designed to withdraw the other therapies.

The primary endpoint of the study is assessment of systolic blood pressure (SBP) profile over the first six hours of treatment. Other key study measurements include measures of cardiac function, SBP changes at specified timepoints, the vasopressor-inotrope score, avoidance of progression to SCAI Stage D or E cardiogenic shock and need for mechanical cardiac support, time to treatment failure, arrhythmia assessments, days alive and out of the hospital through day 30, physiologic measures (e.g., cardiac index) and length of stay in the intensive care unit and hospital.

A data review after enrollment of about 20 participants with SCAI Stage C cardiogenic shock due to acute decompensated heart failure is planned for late 1Q25 / early 2Q25, after which WINT expects to update on the number of additional patients and timing needed to complete the study. WINT anticipates that the data from the SEISMiC C trial will help characterize the potential advantages of istaroxime compared to current standard of care therapies and position istaroxime for Phase 3 readiness in cardiogenic shock and to facilitate its discussions with regulatory agencies to finalize plans for the Phase 3 program design. Windtree expects to interact with regulators in 2025 to transition to a Phase 3 clinical trial.

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Expanding patent position to protect IP, licensing opportunities

Consistent with the company's goal to expand its patent portfolio, protect its IP and also support its licensing opportunities, WINT has been issued several patents for istaroxime. Istaroxime is a novel first-in-class investigational therapy designed to improve systolic contraction and diastolic relaxation of the heart with an overall favorable safety profile and simultaneously boost blood pressure and maintain renal function. Istaroxime has been studied in four positive Phase 2 trials enrolling patients with acute heart failure and early cardiogenic shock due to heart failure and the company is commencing a SCAI trial of the asset.

In the past few weeks, WINT was issued a patent for Istaroxime for Hong Kong through 2039 entitled, "Istaroxime-containing intravenous formulation for the treatment of heart failure (AHF)," application number is 62021023600.1. The claims are directed to istaroxime alone and/or in combination with other agents for the treatment and management of AHF (Acute heart failure).

According to the NIH, "Acute heart failure is broadly defined as a rapid onset of new or worsening signs and symptoms of HF. It is often a potentially life-threatening condition, requiring hospitalisation, and emergency treatment… Mortality post-discharge continues to be high and appears not to have improved significantly over the past decade." Thus, there is significant unmet need associated with AHF.

The patent was issued previously for Japan and another awarded for mainland China. Windtree's licensing partner, Lee's Pharmaceutical intends to launch a Phase 3 program in acute heart failure for its Greater China territory, which Lee is funding. Windtree is collaborating with Lee's on the Phase 3 program and has final signing authority on the protocol. The agreement with Lee's could produce up to $138 million in potential milestone and royalty payments for WINT.

The company intends to continue to optimize its patent portfolio to support Lee's and potentially other future partners in developing Istaroxime and other assets. The company has also filed patent applications in additional markets, including the U.S.. Germany, France and Italy.

Potential partnerships to enhance potential returns

WINT is also developing next generation therapies called SERCA2a activators in areas for acute and chronic cardiovascular disease. In addition, through a recent acquisition, WINT has added a first in class, novel, protein kinase C iota inhibitor oncology platform to its portfolio that includes both topical and oral formulations. The company is optimistic about this platform and intends to move these assets forward in 2024-25. WINT has leveraged strategic M&A to expand its asset portfolio before. Notably, the company acquired its lead asset istaroxime through M&A. To augment its R&D spending, WINT has a regional licensing and research partnership with Lee's Pharmaceutical for greater China and intends to engage in discussions with other large pharma companies for additional potential licensing opportunities. Non-dilutive funds from a possible licensing agreement would be earmarked to support the development of istaroxime and other assets and enable WINT to retain exposure to upside potential if clinical development activities are successful, as expected.

Istaroxime Programs, Early Cardiac Shock Clinical Activities

Istaroxime has two potential lead indications and next generation SERCA2a activator follow-on extensions, including some with oral viability. The company has completed significant preclinical and clinical activities studying istaroxime and has aggregated a database suggesting that the drug is positioned to be a better treatment for early cardiogenic shock and low blood pressure acute heart failure patients. Specifically, istaroxime has been evaluated in multiple studies, including four Phase 2 clinical trials. Results suggest that istaroxime significantly improves cardiovascular physiology with minimal adverse effects. Istaroxime treatment has shown improvement in cardiac function, decreases in PCWP (pulmonary capillary wedge pressure), maintains or reduces heart rate and increases systolic blood

pressure (which is a desired effect in those with normal to low blood pressure) without adverse events such as heart rhythm disturbances – arrhythmia – or heart muscle damage. The most common adverse complaint associated with istaroxime treatment is nausea, particularly at the highest dose, and discomfort at the infusion site.

Multi-Asset / Indication Pipeline with Several Near-Term Milestones

Product Candidates	Indication	Phase	Development Status / Plans
Istaroxime (SERCA2a activator/ Na/K ATPase inhibitor)	**Cardiogenic Shock**	**Phase 2b**	• **Positive Phase 2b studies** • **Executing small follow-on studies intended to transition to Phase 3**
Istaroxime	Acute Heart Failure	Phase 2b	• Positive Phase 2a and 2b data • Greater China regional license with **Lee's Pharma who is advancing and paying for Phase 3 AHF program in territory**
SERCA2a Activators (oral)	Chronic Heart Failure, including potentially HFpEF	Preclinical	• Chronic and Acute Heart Failure • Target for collaboration/partnership
aPKCi inhibitor (topical and oral)	**Cutaneous and systemic treatment in broad and/or rare malignant diseases**	Preclinical	• **IND enabling studies**
Rostafuroxin	Treatment Resistant Hypertension – Genotypically identified patients	Phase 2b	• Phase 2 data in hypertension • Company holding development to out-license and reposition for the attractive and large Resistant Hypertension market
KL4 Surfactant and AEROSURF	KL4 surfactant Drug/Device Tx for RDS and potential other applications	Phase 2b	• **Global out-license in place** • Partner responsible for all costs of development

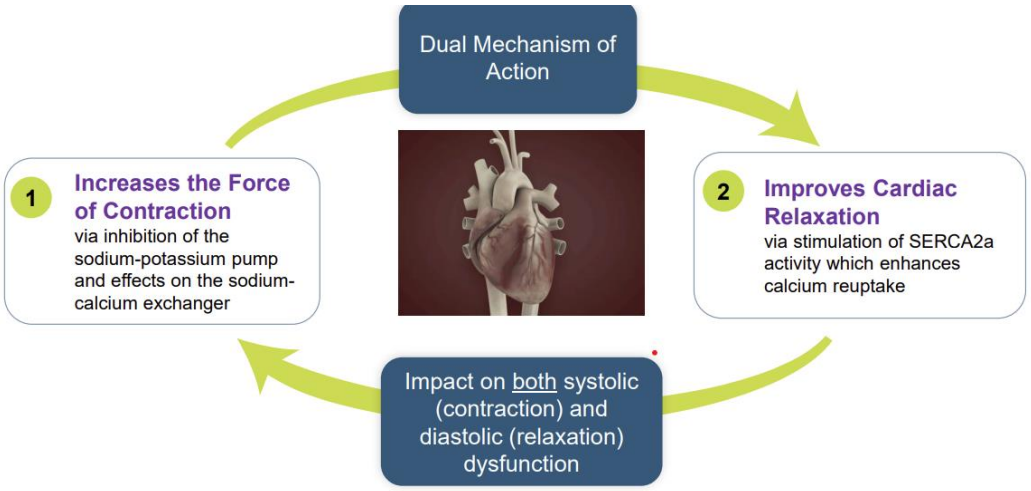
Source: Company reports

Due to the positive effects observed in earlier istaroxime studies on cardiac function and blood pressure, WINT is studying istaroxime for treatment of early cardiogenic shock due to heart failure. The company believes it might have an attractive regulatory pathway for cardiac shock. Moreover, given the unfortunate incidence of cardiac shock (see below), the potential commercial market is large, at an estimated $1.25 billion worldwide. Overall, WINT is prioritizing its cardiac shock program reflect several factors, including that the company believes:

- There are not any suitable drug therapies on the market currently
- There are also no other drugs in development for cardiogenic shock other than istaroxime
- Cardiogenic shock represents an estimated $1.25 billion global market
- It might have a favorable regulatory pathway of increasing blood pressure as a pivotal endpoint

Why has Istaroxime been shown effective? Better squeeze pumps more blood to the heart; relaxation allows heart to fill more effectively

Istaroxime's innovative dual mechanisms of action impact both systolic and diastolic dysfunction. By inhibiting the sodium-potassium ATPase, istaroxime creates a stronger contraction. By stimulating SERCA2a activity, istaroxime also aids the heart in relaxing between contractions, allowing it to fill with blood more effectively. This dual effect on both contraction and relaxation creates a stronger pumping action with a greater amount of blood ejected with each heartbeat. This dual mechanism of action is a key differentiator for istaroxime.



Source: Company reports

In simple terms, unlike many other commercially available agents, istaroxime improves cardiac systolic and diastolic function with an increase (rather than decrease) in systolic blood pressure and has a generally positive profile on renal function. Moreover, there has not been a negative effect on heart rhythm / arrythmias profile, a lower heart rate (which is generally desired) and no measure of cardiac muscle injury, which is another important differentiator from many other agents.

Istaroxime inhibits the sodium-potassium ATPase activity, which makes more calcium available to improve myocardial contractility (inotropic). Istaroxime also activates the SERCA2a, which acts to decrease intracellular calcium by pumping it into sarcoplasmic reticulum (SR) after a contraction. This relaxes the heart muscle, which in turn allows the ventricle to fill more effectively for the next contraction. In combination, these mechanisms produce a stronger contraction and improved cardiac function.

Istaroxime Market Opportunity for Cardiogenic Shock is an estimated $1.25B globally

There have been no significant advances in effective cardiac therapies in decades, implying that istaroxime could fill multiple niches, including cardiac shock. Moreover, the company believes there is no other potentially competitive therapies in active development. Cardiac shock is caused by severe impairment of myocardial performance that leads to reduced cardiac output, organ hypoperfusion, and hypoxia, according to the Journal of the American Heart Association (JAHA). It is a severe presentation of heart failure characterized by extremely low blood pressure and hypo-perfusion to critical organs and generally damages the heart and compromises organ function, including renal activity.

According to the CDC, roughly 6.5 million adults in the U.S. have heart failure. Of these, about 50% are expected to die within five years of diagnosis; AHF and low cardiac output also increase the risk of other organ dysfunction such as renal failure noted above. The disease costs the country more than $30 billion per annum in medical treatment and hospital stays and work days missed.

According to the National Institute of Health (NIH), globally at least 26 million people are affected with heart failure where the heart cannot pump blood at the rate the body needs. The most critical presentation of heart failure, acute heart failure (AHF), requires immediate treatment in a hospital to stabilize the patient. Stabilization is usually achieved using strong intravenous diuretics and could require an intensive care unit and treatment that can take many days. The clinical goal is to get the patient out of crisis, resolve the fluid overload and improve the patient's condition in order to allow the patient to be discharged in a condition to decrease their risk of being readmitted and begin out-patient chronic therapies.

Cardiogenic shock is an area of extreme unmet need. Based on data from multiple sources, cardiogenic shock represents an estimated $1.25 billion global market, as noted, of which the US + EU represent a combined roughly $1.0 billion. The company believes this patient segment represents a significant

opportunity for istaroxime because the drugs that are available currently generally have negative side effects and can result in poor outcomes. Even following stabilization treatments, the risk of mortality remains high, with associated mortality and morbidity of approximately 20-30%.

2nd Istaroxime Program – AHF: Partner, Lee's Pharmaceutical, Conducting Clinical Activities

WINT's licensing partner, Lee's Pharmaceutical, is preparing to embark on a Phase 3 acute heart failure study, following two Phase 2 global studies in which istaroxime consistently demonstrated significant improvement in cardiac function of a failing heart plus significant improvement in blood pressure.

Istaroxime highlights

- Cardiogenic shock – potential for a faster and less expensive path to approval
- Istaroxime has fast track designation for AHF
- Acute Heart Failure represents a second program
- First in class, dual mechanism clinical-stage therapeutic for heart failure that can improve both systolic contractions of the heart, as well as its diastolic relaxation.
- The mechanism includes SERCA2a activation mediated control of heart relaxation:
    - This represents a differentiator for this therapy
    - Also presents opportunities for oral formulation and at-home treatment of chronic conditions

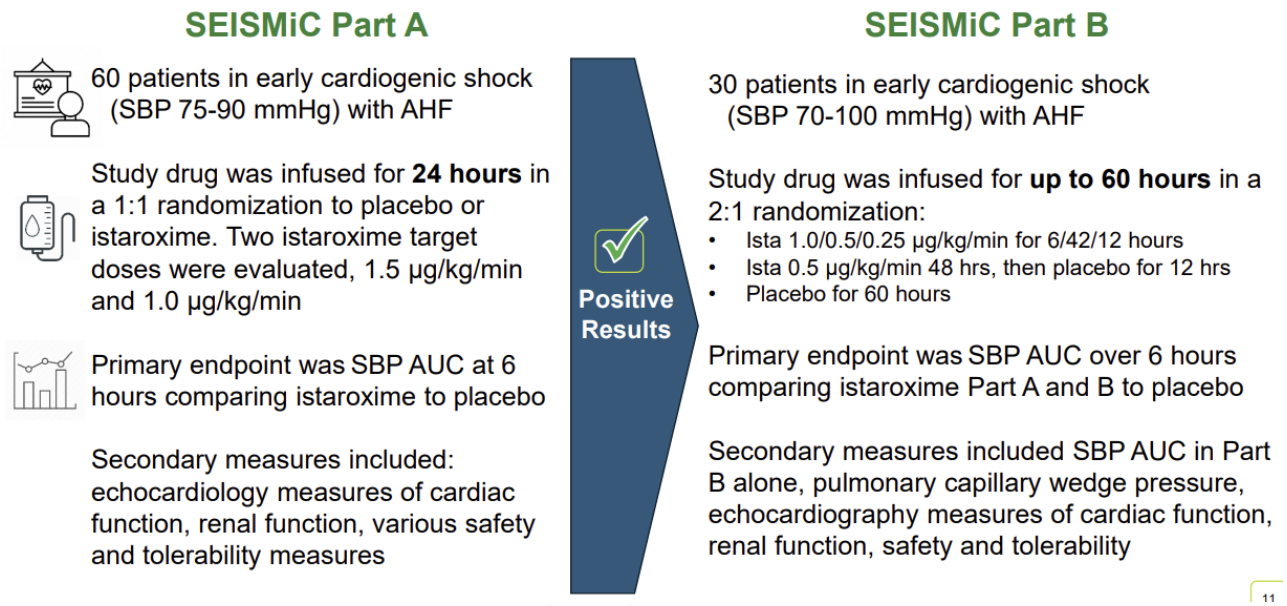
Extension programs leverage Istaroxime's ability to improving cardiac function; SERCA2a Activation for Chronic and Acute Heart Failure

As noted, istaroxime forms the core of the company's heart failure programs, but there are also next generation follow-on compounds, with SERCA2a stimulatory activity that WINT has in preclinical stages of development. WINT hopes to develop these compounds to be potential oral (with potential intravenous administration) therapies for AHF and/or chronic HF (CHF). The company is in discussions with pharmaceutical companies for potential partnering and/or licensing opportunities with SERCA2a activators.

The company believes that each of its clinical programs addresses a large unmet need and provides another avenue of potential regulatory approval from the FDA. For example, the company is studying oral SERCA2a compounds, which is the unique mechanism of istaroxime, for chronic heart failure and possibly for AHF. Together with Istaroxime, these drug candidates create a heart failure platform that WINT intends to advance and also believes can be attractive to potential licensing and/or R&D partners in Big Pharma, while also enabling WINT to retain exposure to upside commercialization potential.

Results of Phase 2b istaroxime study in early cardiogenic shock promising

The company recently conducted a Phase 2b SEISMiC extension study of istaroxime in early cardiogenic shock in the U.S., Europe and Latin America that enrolled hospitalized patients with SCAI Stage B cardiogenic shock with persistent hypotension due to acute heart failure. WINT recently released positive topline data from both Part A and Part B of this extension study that support further clinical efforts. Istaroxime was shown to significantly improve the primary endpoint of the systolic blood pressure profile over six hours. This is a critical clinical objective in treating patients in early cardiogenic shock due to heart failure. Istaroxime also demonstrated significant improvements in many secondary endpoints. These results follow positive results in a previous Phase 2 SEISMiC trial. It also provided information to help further inform dose optimization and the characterization of istaroxime's mechanism of action including potential benefits of SERCA2a activation.



Source: Company reports

The trial evaluated two different dose regimens of istaroxime compared to placebo. Patients received infusions of istaroxime for up to 60 hours. By comparison, treatment in prior studies was limited to 24 hours. The extended treatment time was designed to determine the potential for additional benefit at longer dosing. The trial had one cohort that received a decreasing istaroxime dose over the period and the other cohort received a constant istaroxime dose. It aggregated data related to both cardiac and renal function and additional safety information on cardiac arrhythmias. Importantly, the study results were consistent with results of prior clinical activity, indicating that istaroxime is not related to increased cardiac arrhythmias. WINT believes this is a potentially important differentiating characteristic compared to commonly used current drug therapies.

Study met its primary endpoint

The study met its primary endpoint in significantly improving systolic blood pressure over six hours, with a favorable safety profile that was consistent with earlier clinical trial results, as well as significant benefits in many secondary endpoints also. Both istaroxime cohorts performed significantly better compared to the placebo group.

Study highlights:

- **Significantly improved systolic blood pressure** over six hours of istaroxime dosing (SBP AUC). The combined Part A and Part B SEISMiC istaroxime group performed better versus the placebo group (62.0±7 vs 36.4±7 mmHg*hr, p = 0.0070). The SBP AUC in SEISMiC Part B alone was also significantly improved compared to placebo (78.4±12 vs. 39.6±14 mmHg*hr, p=0.0429), despite a smaller number of patients enrolled in SEISMiC Part B.
  In the combined Part A and Part B analysis, improvements in SBP AUC at 24 hours were also significantly increased in the istaroxime group (292.4±24 vs 190.9±26 mmHg*hr, p=0.0031).

- in Part B alone, which had longer dosing, the istaroxime group was also significantly improved when compared to the placebo group (299.3±48 vs 139.0±56mmHg*hr, (p = 0.0377). The SBP AUC was significantly improved

  - At 48 hours (594.4±95 vs 271.7±110, p = 0.0352) and
  - At 60 hours (711.4±119 vs 320.4±138 mmHg*hr, p = 0.0408).

SEISMiC Part B results:

Cardiac output was improved in the istaroxime group. Over the treatment period, the amount of blood pumped by the heart per minute, or cardiac output[1], was improved during the infusion by about 15% in the istaroxime group. There was no statistically significant increase in heart rate versus placebo in the istaroxime group and heart rate tended to decrease. At 12 and 24 hours, patients in the istaroxime group experienced statistically significant reductions in heart rate (p = 0.0102 and p = 0.0218, respectively).

- **Istaroxime treatment reduced PCWP more than placebo.** This patient population generally has elevated pulmonary capillary wedge pressure (PCWP[2]) and the study participants were consistent with this at baseline. Istaroxime reduced PCWP significantly more than placebo within six hours (-6.6 vs -0.9 mmHg, p = 0.0001), with the effect lasting through 60 hours.
- **Organ perfusion, as assessed by mixed venous oxygen saturation (SVO2[3]), was significantly improved** by 12 hours (mean difference of the istaroxime group compared to placebo was approximately 9%, p=0.0071), and remained significant through 48 hours (p=0.0001) and generally persisted through a 60-hour assessment.
- **Renal function was improved.** Renal function measured by estimated glomerular filtration rate (eGFR) was improved in the istaroxime group compared to placebo at all time points, reaching statistical significance at 48 hours (p =0.0291).
- Clinical signs and symptoms of congestion and heart failure improved in both groups. The New York Heart Association (NYHA) classification of heart failure severity significantly decreased in the istaroxime group at 24 hours (p=0.020), 48 hours (p=0.035), and 72 hours (p=0.010) and was similar to placebo at 96 hours. Moreover, worsening heart failure reported as a serious adverse event occurred less frequently in the istaroxime group compared to placebo (5.3% versus 18.2%, respectively).

The istaroxime safety profile in Part B was favorable and generally consistent with what has been previously reported in other istaroxime clinical trials. Treatment-emergent adverse events were reported more frequently in the istaroxime group at 78.9% compared to 45.5% in the placebo group, predominantly due to nausea, vomiting, infusion site discomfort and headache that have been observed previously with istaroxime. Serious adverse events were infrequent and occurred at a similar frequency in both the istaroxime and placebo groups (10.5% vs. 27.3%, respectively). Importantly, consistent with previous findings, istaroxime did not increase clinically significant arrythmias compared to the placebo group.

KOLs, Cardiologists Support WINT's Optimism

The results of this latest study and the company's growing istaroxime database support WINT's confidence that istaroxime could be a better way to treat AHF and cardiac shock patients. Moreover, WINT's scientific board and KOLs are optimistic about the prospects for istaroxime. Of 100 cardiologists surveyed, 84% indicated that they would be 'likely to extremely likely' to use istaroxime for early cardiogenic shock patients. Moreover, most indicated they would prioritize istaroxime before using other existing classes of therapies such as inotropes and vasopressors.

When asked what the ideal treatment for cardiogenic shock due to heart failure would look like, the responses indicated many of the attributes that characterize istaroxime, including that it:

[1] An increasing heart rate puts upward pressure on cardiac oxygen demand and workload and can therefore lead to harmful effects in heart failure patients.
[2] When PCWP, a measure of cardiac filling pressure, is high, it contributes to worsening heart failure and pulmonary edema.
[3] A low SVO2 can be an indication that cardiac output is not high enough to meet the tissue oxygen needs.

- Improves systolic and diastolic cardiac function, which are the underlying cause of cardiogenic shock
- Improves blood pressure and organ perfusion
- Avoids harmful side-effects to kidney function and to the kidneys
- Does not increase heart rate or increase myocardial oxygen demand or energy requirements of the heart
- Does not increase or cause cardiac arrhythmias
- Contributes to effective diuresis and resolving fluid overload in lungs and body
- Rapid onset of action with a predictable effect that can be titrated to individual patients

Multiple upcoming potential milestones

As discussed above, Windtree is executing multiple clinical programs that lay the groundwork for many potential milestones and catalysts. Among the various upcoming milestones the company expects to report results from its small Phase 2 cardiogenic shock SCAI Stage C study in early 2Q25 and prepare for Phase 3 readiness later in 2025. The company also expects its license partner Lee's Pharma to launch a Phase 3 Acute Heart Failure study in Asia/PAC, working closely with Windtree. In addition, WINT expects to secure additional licenses for istaroxime and SERCA2a activators to augment its financial flexibility to advance its assets. In addition, Windtree intends to provide a business update for the preclinical oncology aPKCi inhibitors to progress toward IND enablement later this year.

Risks

Risks include that the competitive landscape could change, although management believes that istaroxime is the only therapy in development for the indications discussed above. In addition, the company's plans could incur higher costs than currently anticipated and WINT might have to raise funds that could be dilutive to existing shareholders, among other risks.

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