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UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
WASHINGTON, D.C. 20549

FORM 10-K

☒ **ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**

For the fiscal year ended **December 31, 2021**

Or

☐ **TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**

For the transition period from _____ to _____

Commission **File Number**: 000-26422

WINDTREE THERAPEUTICS, INC.

(Exact name of registrant as specified in its charter)

Delaware	**94-3171943**
(State or other jurisdiction of incorporation or organization)	(I.R.S. Employer Identification No.)
2600 Kelly Road, Suite 100 **Warrington, Pennsylvania** (Address of principal executive offices)	**18976-3622** (Zip Code)

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

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

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

Securities registered pursuant to Section 12(g) of the Act:
None

Indicate by check mark if the registrant is a well-known seasoned issuer, as defined in Rule 405 of the Securities Act. Yes ☐ No ☒

Indicate by check mark if the registrant is not required to file reports pursuant to Section 13 or Section 15(d) of the Exchange Act. Yes ☐ No ☒

Indicate by check mark whether the registrant: (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days. Yes ☒ No ☐

Indicate by check mark whether the registrant has submitted electronically every Interactive Data File required to be submitted pursuant to Rule 405 of Regulation S-T (§ 232.405 of this chapter) during the preceding 12 months (or for such shorter period that the registrant was required to submit such files). Yes ☒ No ☐

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, smaller reporting company, or an emerging growth company. See the definitions of "large accelerated filer," "accelerated filer," "smaller reporting company," and "emerging growth company" in Rule 12b-2 of the Exchange Act.

Large accelerated filer ☐ Accelerated filer ☐

Non-accelerated filer ☒ Smaller reporting company ☒

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. ☐

Indicate by check mark whether the registrant has filed a report on and attestation to its management's assessment of the effectiveness of its internal control over financial reporting under Section 404(b) of the Sarbanes-Oxley Act (15 U.S.C. 7262(b)) by the registered public accounting firm that prepared or issued its audit report. ☐

Indicate by check mark whether the registrant is a shell company (as defined in Rule 12b-2 of the Exchange Act). Yes ☐ No ☒

On June 30, 2021, the aggregate market value of shares of voting and non-voting common equity held by non-affiliates of the registrant was approximately $44.1 million (based on the closing price on The Nasdaq Capital Market on that date). In determining this amount, the registrant has assumed solely for this purpose that all of its directors, executive officers and persons beneficially owning 10% or more of the outstanding shares of common stock of the registrant may be considered to be affiliates. This assumption shall not be deemed conclusive as to affiliate status for this or any other purpose.

As of March 30, 2022, there were 28,469,274 shares of the registrant's common stock issued and outstanding.

Unless the context otherwise requires, all references to "we," "us," "our," and the "Company" include Windtree Therapeutics, Inc., and its consolidated subsidiaries.

DOCUMENTS INCORPORATED BY REFERENCE

Part III of this Annual Report on Form 10-K incorporates certain information by reference from the registrant's proxy statement for the annual meeting of stockholders to be filed no later than 120 days after the end of the registrant's fiscal year ended December 31, 2021.

FORWARD-LOOKING STATEMENTS

This Annual Report on Form 10-K contains "forward-looking statements" within the meaning of Section 27A of the Securities Act of 1933, as amended, or the Securities Act, and Section 21E of the Securities Exchange Act of 1934, as amended, or the Exchange Act. These 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. Forward-looking statements are subject to many risks and uncertainties that could cause actual results to differ materially from any future results expressed or implied by the forward-looking statements. We caution you therefore against relying on any of these forward-looking statements. They are neither statements of historical fact nor guarantees or assurances of future performance. Examples of such risks and uncertainties, which potentially could have a material adverse effect on our development programs, business and/or operations, include, but are not limited to the following:

- our estimates regarding future results of operations, financial position, research and development costs, capital requirements and our needs for additional financing;
- how long we can continue to fund our operations with our existing cash and cash equivalents;
- delays in our anticipated timelines and milestones and additional costs associated with the impact of the residual effects of the novel coronavirus, or COVID-19, pandemic, or with the impact of the geopolitical instability (including the ongoing military conflict between Russia and Ukraine), on our clinical trial operations;
- the costs, timing, and results, of our preclinical studies and clinical trials, as well as the number of required trials for regulatory approval and the criteria for success in such trials;
- legal and regulatory developments in the United States, or U.S., and foreign countries, including any actions or advice that may affect the design, initiation, timing, continuation, progress or outcome of clinical trials or result in the need for additional clinical trials;
- the difficulties and expenses associated with obtaining and maintaining regulatory approval of our product candidates, and the indication and labeling under any such approval;
- our plans and the plans of our licensee, Lee's Pharmaceutical (HK) Ltd., or Lee's (HK), in Asia and our respective abilities to successfully execute necessary clinical and business development activities in a timely manner, if at all, to support development and commercialize our product candidates;
- risks related to manufacturing active pharmaceutical ingredients, or APIs, drug product, medical devices and other materials we need;
- delays, interruptions or failures in the manufacture and supply of our product candidates;
- the performance of third parties, both foreign and domestic, upon which we depend, including contract research organizations, or CROs, contract manufacturing organizations, or CMOs, contractor laboratories and independent contractors;
- the size and growth of the potential markets for our product candidates, the regulatory requirements in such markets, the rate and degree of market acceptance of our product candidates and our ability to serve those markets;
- the success of competing therapies and products that are or become available;

- our ability to limit our exposure under product liability lawsuits;
- our ability to obtain and maintain intellectual property protection for our product candidates;
- recently enacted and future legislation regarding the healthcare system in the U.S. or the healthcare systems in foreign jurisdictions;
- our ability to recruit or retain key scientific, commercial or management personnel or to retain our executive officers;
- our ability to secure electronically stored work product, including clinical data, analyses, research, communications and other materials necessary to gain regulatory approval of our product candidates, including those acquired from third parties, and assure the integrity, proper functionality and security of our internal computer and information systems and prevent or avoid cyber-attacks, malicious intrusion, breakdown, destruction, loss of data privacy or other significant disruption;
- the impact of the significant impairment of our intangible assets on our consolidated balance sheet, and any future impairment charges that may be reported; and
- economic uncertainty resulting from geopolitical instability, including the ongoing military conflict between Russia and Ukraine.

Pharmaceutical, biotechnology and medical technology companies have suffered significant setbacks conducting clinical trials, even after obtaining promising earlier preclinical and clinical data. In addition, data obtained from clinical trials are susceptible to varying interpretations, which could delay, limit or prevent regulatory approval. After gaining approval of a drug product, medical device or combination drug/device product, pharmaceutical and biotechnology companies face considerable challenges in marketing and distributing their products and may never become profitable.

The forward-looking statements contained in this report or the documents incorporated by reference herein speak only as of their respective dates. Factors or events that could cause our actual results to differ may emerge from time to time and it is not possible for us to predict them all. Except to the extent required by applicable laws, rules or regulations, we do not undertake any obligation to publicly update any forward-looking statements or to publicly announce revisions to any of the forward-looking statements, whether as a result of new information, future events or otherwise.

RISK FACTOR SUMMARY

The risk factors summarized and detailed below could materially harm our business, operating results and/or financial condition, impair our future prospects and/or cause the price of our common stock to decline. These are not all of the risks we face, and other factors not presently known to us or that we currently believe are immaterial may also affect our business if they occur. The following is a summary of the material risks that may affect our business, operating results and financial condition include, but are not necessarily limited to, those relating to:

Risks Related to Our Financial Condition

- We will require substantial additional financing to achieve our goals, and a failure to obtain this necessary capital when needed on acceptable terms, or at all, could force us to delay, limit, reduce or terminate our product development programs, or other operations.
- Our losses, negative cash flows from operations, and accumulated deficit raise substantial doubt about our ability to continue as a going concern absent obtaining adequate new debt or equity financings.
- Unstable market and economic conditions may have serious adverse consequences on our business, financial condition, and stock price.
- Due to the significant resources required to develop each of our product candidates, we must prioritize development of certain product candidates and/or certain disease indications. We may be delayed in advancing a product candidate if our plan does not include sufficient funding to execute a clinical program. If we expend our limited resources on candidates or indications that do not yield a successful product and fail to capitalize on other product candidates or indications that may be more profitable or for which there is a greater likelihood of success, such failure could have a material adverse effect on our business, financial condition, results of operations, and prospects.
- We may never realize the full value of our intangible assets.

Risks Related to our Development Activities and Regulatory Approval of our Product Candidates

- We are substantially dependent on the success of our lead product candidate, istaroxime. To the extent that our clinical development of istaroxime is not successful, our business, financial condition, and results of operations may be materially adversely affected and the price of our common stock may decline.
- We have limited experience with the development of therapies targeted to the treatment of early cardiogenic shock and COVID-19-related acute lung injury and may not succeed in our efforts to gain approval of our product candidates and establish a profitable business.
- Delays in clinical trials are common and have many causes, and any delay could result in increased costs to us and jeopardize or delay our ability to obtain regulatory approval and commence product sales or allow for competition to emerge.
- The COVID-19 pandemic has negatively impacted, and may continue to negatively impact our ability to develop our product candidates.
- Use of our product candidates could be associated with side effects, adverse events or other properties or safety risks, which could delay or preclude approval, cause us to suspend or discontinue clinical trials, abandon a product candidate, limit the commercial profile of an approved label or result in other significant negative consequences that could severely harm our business, prospects, operating results and financial condition.
- Although we may pursue expedited regulatory programs for a product candidate or an indication, it may not qualify for expedited development or, if it does qualify for expedited development, it may not actually lead to a faster development or regulatory review or approval process.
- Interim, topline and preliminary data from our clinical trials that we announce or publish from time to time may change as more patient data become available and are subject to audit and verification procedures that could result in material changes in the final data.
- We have conducted, and may in the future conduct, clinical trials for our product candidates at clinical sites located in the U.S. and outside of the U.S. If the FDA and other foreign equivalents raise concerns about certain of the clinical sites based on location and regulatory environment, they may not accept data from such trials, in which case our development plans will be delayed, which could materially harm our business.
- If the FDA or other applicable regulatory authorities approve generic products with claims that compete with our product candidates, it could reduce our sales of our product candidates if approved.
- The successful commercialization of our product candidates, if approved, will depend in part on the extent to which governmental authorities and health insurers establish coverage, adequate reimbursement levels and favorable pricing policies. Failure to obtain or maintain coverage and adequate reimbursement for our product candidates could limit our ability to market those product candidates and decrease our ability to generate revenue.

Risks Related to Our Reliance on Third Parties

- We rely on third parties, primarily outside of the U.S., to conduct many of our preclinical studies and clinical trials. Any failure by a third party to conduct the clinical trials according to good clinical practices, or GCPs, and other requirements and in a timely manner may delay or prevent our ability to seek or obtain regulatory approval for or commercialize our product candidates.

- We plan to rely on third parties, some of which are located outside the U.S., to manufacture our drug product candidates, which exposes us to risks that may affect our ability to maintain supplies of our clinical materials, and subject us to uncertainty associated with the international political climate, and could potentially delay our research and development activities, as well as eventual regulatory approval and commercialization of our drug product candidates.

Risks Related to our Business and Operations

- Our operating results may fluctuate significantly, which makes our future operating results difficult to predict and could cause our operating results to fall below expectations or any guidance we may provide.
- We are continually evaluating our business strategy and may modify this strategy to respond to developments in our business and other factors, and any such modification, if not successful, could have a material adverse effect on our business, financial condition, and results of operations.
- The political and healthcare policy and reimbursement environment is becoming more challenging for pharmaceutical companies and medical device manufacturers and may adversely affect our business.
- We depend upon key employees and consultants in a competitive market for skilled personnel. If we or our strategic partners or collaborators are unable to attract and retain key personnel, it could adversely affect our ability to develop and market our product candidates.
- We could be adversely affected by any interruption, including from breaches in cybersecurity, in our ability to conduct business at our current location.

Risks Related to Government Regulation

- Our activities are subject to various and complex laws and regulations, and we are susceptible to a changing regulatory environment. Violations or allegations of violations of these laws may result in large civil and criminal penalties, debarment from participating in government programs, diversion of management time, attention and resources and may otherwise have a material adverse effect on our business, financial condition and results of operations.
- Failure in our information technology systems could disrupt our operations and cause the loss of confidential information and business opportunities.
- Healthcare reform measures in the U.S., as well as the general tightening of drug reimbursement pathways and levels of reimbursement globally, are expected to add additional pressure to achieve financial expectations for our product candidates, if approved.
- Our international operations subject us to additional regulatory oversight in foreign jurisdictions, as well as economic, social, and political uncertainties, which could cause a material adverse effect on our business, financial position, and operating results.
- Our employees and independent contractors, including principal investigators, CROs, consultants and vendors, may engage in misconduct or other improper activities, including noncompliance with regulatory standards and requirements.
- We are subject to anti-bribery, anti-corruption, and anti-money laundering laws, including the U.S. Foreign Corrupt Practices Act, in which violations of these laws could result in substantial penalties and prosecution.
- We and any of our third-party manufacturers or suppliers may use potent chemical agents and hazardous materials, and any claims relating to improper handling, storage or disposal of these materials could be time consuming or costly.

Risks Related to Intellectual Property Matters

- If we cannot protect our intellectual property, others could use our technology in competitive products. Even if we obtain patents to protect our product candidates, those patents may not be sufficiently broad, or they may expire and others could then compete with us.
- Intellectual property rights of third parties could limit our ability to develop and market our product candidates.
- We rely on agreements containing obligations regarding intellectual property, confidentiality and noncompetition provisions that could be breached and may be difficult to enforce.
- Intellectual property rights do not necessarily address all potential threats.

Risks Related to the Ownership of our Securities

- A small group of our investors, including Lee's Pharmaceutical Holdings Limited, or Lee's Holdings, may be able to exercise significant influence over our business strategy and operations.
- Our common stock is listed on the Nasdaq Capital Market. We can provide no assurance that we will be able to comply with the continued listing requirements over time and that our common stock will continue to be listed on the Nasdaq Capital Market.
- Our Certificate of Incorporation provides that the Court of Chancery of the State of Delaware will be the exclusive forum for substantially all disputes between us and our stockholders, which could limit our stockholders' ability to file in a different judicial forum to resolve disputes with us or our directors, officers or employees.

WINDTREE THERAPEUTICS, INC.

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For the Fiscal Year Ended December 31, 2021

PART I

ITEM 1. BUSINESS.

Overview

We are a clinical-stage biopharmaceutical company focused on the development of novel therapeutics intended to address significant unmet medical needs in important acute care markets. Our development programs are primarily focused in the treatment of acute cardiovascular and secondarily in acute pulmonary diseases. Our lead product candidate, istaroxime, is a first-in-class, dual-acting agent being developed to improve cardiac function in patients with acute heart failure, or AHF, with a potentially differentiated safety profile from existing treatments. Istaroxime demonstrated significant improvement in both diastolic and systolic aspects of cardiac function and was generally well tolerated in two phase 2 clinical trials. Istaroxime has been granted Fast Track designation for the treatment of AHF by the U.S. Food and Drug Administration, or FDA. Based on the profile observed in our phase 2 clinical studies in AHF, where istaroxime significantly improved cardiac function and systolic blood pressure in acute decompensated heart failure patients, we initiated a phase 2 global clinical study to evaluate istaroxime for the treatment of early cardiogenic shock (Society for Cardiovascular Angiography and Interventions Stage B shock), a severe form of heart failure characterized by very low blood pressure and risk for hypoperfusion to critical organs. We believe that istaroxime has the potential to fulfill an unmet need in early cardiogenic shock. Our heart failure cardiovascular portfolio also includes sarco endoplasmic reticulum Ca2+ -ATPase 2a, or SERCA2a, activators which activate SERCA2a. This research program is evaluating these preclinical product candidates, including oral and intravenous SERCA2a activator heart failure compounds. As potential oral agents, these candidates would be developed for chronic heart failure. In addition, our cardiovascular drug product candidates include rostafuroxin, a novel product candidate for the treatment of hypertension in patients with a specific genetic profile. We are pursuing potential licensing arrangements and/or other strategic partnerships and do not intend to advance this product candidate without securing such an arrangement or partnership.

Our pulmonary product candidate portfolio consists of a KL4 surfactant platform to address a range of serious respiratory conditions in children and adults. KL4 surfactant has been in development as a liquid instillate for noninvasive delivery as an aerosol. In September 2020, the FDA accepted our investigational new drug, or IND, application for an open-label phase 2 pilot study to assess safety and tolerability in the COVID-19 acute respiratory distress syndrome, or ARDS, population and the ability of our KL4 surfactant liquid instillate to impact key respiratory parameters in the treatment of lung injury and ARDS resulting from severe acute respiratory syndrome coronavirus 2, or SARS-CoV-2, the causative agent in novel coronavirus, or COVID-19, infections. In January 2022, we completed enrollment of 20 patients in our phase 2 study of lucinactant (KL4 surfactant) for patients with severe COVID-19 associated ARDS and lung injury. The study demonstrated that intratracheal administration of reconstituted lyophilized lucinactant was generally safe and well tolerated. Lucinactant was safely administered to critically ill, mechanically ventilated patients with severe COVID-19 associated ARDS. Oxygenation and other physiological parameters were stable to improved after dosing, supporting the feasibility of this treatment approach to develop a potential treatment for critically ill patients with ARDS due to COVID-19 or other causes.

Previously, we were also developing AEROSURF (lucinactant for inhalation), a novel drug/medical device combination product for noninvasive delivery of aerosolized KL4 surfactant using our ADS technology for the treatment of respiratory distress syndrome, or RDS, in premature infants. We suspended all internal AEROSURF clinical activities in November 2020, because istaroxime, our lead product candidate, has become our primary focus for investment and execution as we believe development of istaroxime represents a greater value opportunity for us and our stockholders than development of KL4 surfactant. Since completing our phase 2 study of lucinactant (KL4 surfactant) for patients with severe COVID-19 associated ARDS and lung injury in January 2022, in order to preserve resources for the highest priority programs, we have begun to reduce costs that were not already transferred to our licensee in Asia, Lee's Pharmaceutical (HK) Ltd., or Lee's (HK), under the terms of our License, Development and Commercialization Agreement between us and Lee's (HK) dated as of June 12, 2017, as amended, or the Asia License Agreement. These costs include certain reductions in headcount dedicated to KL4 surfactant and the decommissioning of both our analytical and technical support laboratory, which previously conducted release testing of active pharmaceutical ingredients, or APIs, and supportive research for our lyophilized and aerosolized KL4 surfactant, and our medical device development laboratory, which was previously used to conduct development activities and testing for our ADS technologies. To support the future development of our KL4 surfactant platform in markets outside of Asia, including the U.S., we are pursuing one or more licensing transactions.

Our ability to advance our development programs is dependent upon our ability to secure additional capital in both the near and long-term, through public or private equity offerings; through potential strategic opportunities, including licensing agreements, drug product development and marketing collaboration arrangements, pharmaceutical research cooperation arrangements or other similar transactions in geographic markets, including the U.S., and/or through potential grants and other funding commitments from U.S. government agencies, in each case, if available. We have engaged with potential counterparties in various markets and will continue to pursue non-dilutive sources of capital as well as potential private and public offerings. There can be no assurance, however, that we will be able to identify and enter into public or private securities offerings on acceptable terms and in amounts sufficient to meet our needs or qualify for non-dilutive funding opportunities under any grant programs sponsored by U.S. government agencies, private foundations and/or leading academic institutions, or identify and enter into any strategic transactions that will provide the additional capital that we will require. If none of these alternatives is available, or if available, we are unable to raise sufficient capital through such transactions, we potentially could be forced to limit or cease our development activities, which would have a material adverse effect on our business, financial condition and results of operations.

Our Development Programs

The table below summarizes the current status and anticipated milestones for our principal product development programs. However, due to the disruptive impact of the COVID-19 pandemic, in the U.S. and globally, and its effect on hospital resources, focus, availability of services, and professional staff, our clinical trials and the next expected milestones of our product candidates may be impacted, and we may experience delays in anticipated timelines and milestones. In addition, these timelines are dependent on our ability to secure sufficient capital to continue development without interruption.

Product Candidate	Indication	Status	Next Expected Milestone
Cardiovascular Programs			
Istaroxime	Early Cardiogenic Shock	Phase 2a	Completed clinical study in 60 patients; topline data expected April 2022.
Istaroxime	AHF	Phase 2b	Ongoing study start-up activities for second phase 2b clinical trial in approximately 300 patients targeted to start once the clinical trial is fully funded.
Oral SERCA2a Activators	Chronic and AHF, including HFpEF	Preclinical	Ongoing preclinical studies; pursuing potential licensing transactions, research partnership arrangements or other strategic opportunities.
Rostafuroxin	Genetically Associated Hypertension	Phase 2b	Pursuing potential out-licensing transactions or other strategic opportunities.
Pulmonary Programs			
Lyophilized KL4 Surfactant	COVID-19-associated lung injury and ARDS	Phase 2a	Enrollment of 20 patients is complete; data was announced in the first quarter of 2022 and showed that the product candidate was generally safe and well tolerated with stable to improved oxygenation and other physiological parameters after dosing.
AEROSURF (aerosolized KL4 surfactant based on ADS technology)	RDS	Phase 2b	Pursuing one or more licensing transactions in markets outside of Asia, including in the U.S., for RDS and all KL4 surfactant related products.

Cardiovascular Programs

Heart failure is a chronic, progressive condition in which patients often experience episodic periods of increased symptoms known as AHF, where the heart fails to adequately pump, resulting in worsening symptoms, including pulmonary and peripheral edema and other severe complications. In the U.S., approximately 6 million people (nearly 2% of the adult population) have heart failure and approximately half of these patients are expected to die within five years of diagnosis; and in the combined U.S., EU and Japan markets, there are more than 18 million patients suffering from heart failure. Heart failure is the leading cause of hospitalization in patients age 65 years and older. AHF can be precipitated by many factors and puts patients at increased risk for morbidity, hospital readmission and mortality. There are more than 1.3 million hospital admissions for heart failure in the U.S. each year and over 2.5 million hospital estimated admissions for AHF in the combined U.S., EU and Japan markets. We estimate that AHF may represent a potential combined annual addressable market (U.S., EU and Japan) of approximately two million patients with multi-billion-dollar annual market value.

Istaroxime (Early Cardiogenic Shock)

We are evaluating istaroxime for the treatment of early cardiogenic shock, a severe presentation of heart failure characterized by very low blood pressure and risk for hypoperfusion to critical organs which is associated with high mortality and morbidity and is not well treated with current therapies. In September 2020, we initiated a small phase 2 clinical study of istaroxime for the acute treatment of early cardiogenic shock in heart failure patients with a more severe case of heart failure to evaluate the potential to improve blood pressure. The study also will evaluate the safety and side effect profile of istaroxime in this patient population. We expect data to be available in April 2022. The global COVID-19 pandemic has had a disruptive effect on hospital resources (including in intensive care units, or ICUs) where this study is being conducted. The COVID-19 pandemic has impacted the severity of illness of patients presenting with early cardiogenic shock and/or conditions that could lead to early cardiogenic shock. In addition, the geographic mix of patients can impact the outcome of a clinical trial, and with the global spread of COVID-19 occurring in waves, the mix of patients across countries has fluctuated. How these dynamics could potentially impact both timelines and outcomes is unknown.

We believe istaroxime may fulfill an unmet need in early cardiogenic shock based on the profile observed in our phase 2 clinical studies in AHF, which demonstrated that istaroxime significantly improved cardiac function and systolic blood pressure. There is significant unmet medical need in the area of early cardiogenic shock and severe heart failure. If istaroxime is able to demonstrate a meaningful improvement in blood pressure in clinical trials of this condition, we believe there may be an opportunity to apply for a Breakthrough Therapy designation that could provide beneficial opportunities for the development program. We note that regulatory precedent exists for an approval in shock (distributive) based primarily upon improvements in blood pressure with an acceptable safety profile. We will be exploring the potential for this type of pathway for istaroxime. In addition, we believe the receipt of either Fast Track or Breakthrough Therapy designation may increase the likelihood of receiving priority review of a marketing application, which would provide for an expedited review timeframe; however, there is no guarantee that we would receive Breakthrough Therapy or Fast Track designation or that any such designation will lead to a faster development process, review or approval compared to product candidates considered for approval under conventional FDA procedures.

Using cardiogenic shock patient U.S. hospital claims and worldwide prevalence data, we estimate the worldwide total market value of cardiogenic shock to be $1.25 billion. This estimate is calculated by multiplying the patient numbers from the largest markets, by the assumed various regional prices of drug treatment in the acute care market. The addressable market for istaroxime will be a subset of the total market value of $1.25 billion.

Istaroxime (AHF)

Istaroxime is a first-in-class, dual action investigational drug that we are developing to treat AHF with a potentially differentiated safety profile from current AHF therapies. In 2019, we announced topline results of a successful phase 2b clinical trial of istaroxime in which the primary endpoint of cardiac function, E/e' ratio (echocardiographic assessment reflecting changes in pulmonary capillary wedge pressure, or PCWP, or left ventricular filing pressure) as well as other important parameters were significantly improved. Istaroxime has been granted Fast Track designation by the FDA for the treatment of AHF. In April 2020, we announced the presentation at the American College of Cardiology 2020 virtual meeting of a new subset analysis from a phase 2b study of istaroxime in patients hospitalized with AHF. This post-hoc analysis characterized the responses between Caucasian and Asian patients and demonstrated that the istaroxime dose of 0.5 µg/kg/min produced a similar response on E/e', the primary study endpoint, and stroke volume index, an important measure of cardiac performance.

Istaroxime represents a novel approach to the treatment of AHF. It has a dual mechanism of action to improve cardiovascular physiology. Current therapy for heart failure in the hospital typically includes intravenous diuretics and, if the blood pressure is low, supportive therapy with inotropes. Inotropes are often associated with adverse effects such as hypotension, arrhythmias and, in some cases, increased mortality. These drugs are used only if needed to support blood pressure and cardiac function. We believe that istaroxime, if approved, may have the potential to address unmet medical needs of these patients by improving cardiac function and management of fluid accumulation that contributes to heart failure symptoms with a potentially differentiated safety profile from current AHF therapies, including a potential reduction in complications and improvement of other clinical outcomes.

To advance istaroxime for the treatment of AHF potentially through the phase 2 clinical program and be in a phase 3-ready position, our strategy includes, subject to adequate resources, planning an additional phase 2 clinical trial that will enroll approximately 300 patients in approximately 60 clinical sites globally. This trial will focus on treating heart failure patients with low blood pressure, who also tend to be diuretic resistant, as a patient population that we believe could particularly benefit from the unique profile and potential ability of istaroxime to increase cardiac function and increase blood pressure while maintaining or improving renal function.

This trial will also collect data on measures that may serve as primary endpoints in a phase 3 clinical trial, and will include an optimized dosing regimen, potentially extending the infusion time beyond 24 hours. We currently do not have sufficient capital to execute this clinical trial. We are exploring capital from public and private equity offerings and potential strategic opportunities to fund the initiation of this clinical trial, and plan to initiate the clinical trial after obtaining adequate funding. We plan to closely monitor the impact of the COVID-19 pandemic and its impact on hospital resources and resulting potential changes in regulatory timelines for conducting non-COVID-19-related clinical trials.

Rostafuroxin

Rostafuroxin is a novel investigational drug product candidate being developed for the treatment of hypertension in patients with a specific genetic profile, which is found in approximately 20% - 25% of the adult hypertensive population. Rostafuroxin has been studied in three phase 2 clinical trials assessing reduction in blood pressure in a hypertensive population selected in accordance with the specified genetic profile. After positive phase 2a results, a phase 2b study was initiated. In this most recent phase 2b clinical trial, rostafuroxin demonstrated efficacy in Caucasian patients in treatment naïve hypertension. During the second quarter of 2021, we concluded an initial process to test the industry's interest in investing in our drug product candidate. We currently have not been able to secure a licensing transaction or other strategic opportunity. As a result, we recorded an impairment of the related intangible asset (*see*, Note 4 – Accounting Policies and Recent Accounting Pronouncements – Goodwill and Intangible Assets). Based on feedback received from potential licensing partners, we have determined that there is a need for an additional phase 2 clinical trial to demonstrate efficacy in non-Caucasian and Caucasian patients in treatment resistant hypertension. We are continuing to pursue licensing arrangements and/or other strategic partnerships for rostafuroxin. We do not intend to conduct the additional phase 2 clinical trial without securing such an arrangement or partnership.

According to the Centers for Disease Control and Prevention, or the CDC, patients with high blood pressure have a greater risk for heart disease and stroke, which are leading causes of death in the U.S. Nearly half of adults in the U.S. (108 million, or 45%) have hypertension defined as a systolic blood pressure ≥ 130 mm Hg or a diastolic blood pressure ≥ 80 mm Hg or are taking medication for hypertension. In 2018, nearly half a million deaths in the U.S. included hypertension as a primary or contributing cause. Only about 1 in 4 adults (24%) with hypertension have their condition under control. Patients often have persistent hypertension despite being on multiple therapies. Ethnicity and genetic makeup are known to impact the response to anti-hypertensive treatments, and uncontrolled hypertension has been associated with certain genetic makeups. Given the size of the market and the prevalence of unmet medical needs, major pharmaceutical companies have maintained hypertension as a key area of focus and continue to seek new drugs to compete in markets they have established with previous anti-hypertensive therapies.

SERCA2a Activators – Preclinical Oral, Chronic and Acute Heart Failure Product Candidates

We are pursuing several early exploratory research programs to assess potential product candidates, including oral and intravenous SERCA2a activator heart failure compounds, and believe that we can add value to our cardiovascular portfolio by advancing these SERCA2a activator candidates through preclinical studies. To further advance these product candidates, we are actively exploring potential licensing transactions, research partnership arrangements or other strategic opportunities.

Pulmonary Programs

Lyophilized KL4 Surfactant (COVID-19 related Lung Injury)

Patients with COVID-19 pneumonia may progress to severe respiratory failure requiring supplemental oxygen and mechanical ventilation. This acute lung injury, known as ARDS, has no approved therapies and is associated with significant morbidity, mortality and healthcare resource utilization. The COVID-19 virus infects via angiotensin-converting enzyme 2 receptor, or ACE2, on surfactant producing cells in the lung. The ACE2 receptor is found on alveolar Type 2 cells in the lung. Type 2 cells are the source of pulmonary surfactant production. When these cells are infected and damaged, surfactant production is impaired, increasing the risk for respiratory failure as surfactant is necessary for the lungs to stay inflated and for proper gas exchange. Surfactant deficiency is known to contribute to the pathophysiology of ARDS, respiratory failure, and lung injury in patients on mechanical ventilation.

In January 2022, we completed enrollment of 20 patients in our study of lucinactant (KL4 surfactant) for patients with severe COVID-19 associated ARDS and lung injury. The phase 2 trial was designed to assess feasibility, safety, and tolerability of administration of reconstituted lyophilized lucinactant in these critically ill patients. The multicenter, single-arm study enrolled 20 critically ill patients who were intubated and on mechanical ventilation due to severe COVID-19 associated ARDS. Patients received lucinactant as a liquid via the endotracheal tube assessing safety and tolerability of the administration procedure and of the drug. Oxygenation and other physiological responses were also measured. Study sites were in the U.S. and Argentina.

The study demonstrated that intratracheal administration of reconstituted lyophilized lucinactant was generally safe and well tolerated. Lucinactant was safely administered to critically ill, mechanically ventilated patients with severe COVID-19 associated ARDS. Oxygenation and other physiological parameters were stable to improved after dosing, supporting the feasibility of this treatment approach to develop a potential treatment for critically ill patients with ARDS due to COVID-19 or other causes.

AEROSURF (lucinactant for inhalation)

AEROSURF is an investigational combination drug/medical device product to improve the management of RDS in premature infants. RDS is a condition that occurs in premature infants who may not have fully developed natural lung surfactant, which is essential to normal respiratory function and survival, and may require surfactant therapy to sustain life, and can result in long-term respiratory problems, developmental delays and death. Surfactant therapy is the primary therapy to address an underlying surfactant deficiency, and AEROSURF is designed to deliver aerosolized KL4 surfactant noninvasively using our proprietary ADS technology. We have completed three AEROSURF phase 2 clinical trials. Our most recent phase 2b clinical trial did not achieve its primary endpoint, due primarily, we believe, to an unexpected rate of treatment interruptions associated with the prototype phase 2 ADS used in the phase 2b clinical trial, or phase 2 ADS. After excluding patients whose doses were interrupted, in accordance with the predesignated statistical plan, we observed a meaningful treatment effect in line with our desired targeted outcome and believe that these results support the further development of AEROSURF to reduce both the rate of nasal continuous positive airway pressure, or nCPAP, failure and the need for intubation in premature infants being treated for RDS. AEROSURF has been granted Fast Track designation by the FDA for the treatment of RDS.

In August 2020, we entered into a Project Financing Agreement with Lee's (HK), or the PF Agreement, dated and effective as of August 12, 2020, under which we received payments totaling $2.8 million through October 2020. Pursuant to the PF Agreement, Lee's (HK) agreed to pay additional amounts to be set forth in an updated development budget to be agreed between the parties by September 1, 2020 and updated every six months thereafter, to fund the continued development of AEROSURF and to be paid with the payment schedule to be set forth in each updated development budget. In partial satisfaction of our obligations under the PF Agreement, we agreed to pay Lee's (HK) 50% of any Commercialization Net Revenues (as defined in the PF Agreement) up to an amount that is equal to 125% of the Project Expenses (as defined in the PF Agreement) funded by Lee's (HK). On November 12, 2020, Lee's (HK) provided notice of termination of additional funding under the PF Agreement, and we and Lee's (HK) revised our plans for the continued development of AEROSURF. Lee's (HK) agreed to continue the development of AEROSURF in Asia at its own cost. Lee's (HK) agreed to fund an additional $1.0 million to us in 2021 for certain transition and analytical services to be provided by us with respect to the development of AEROSURF, which will be considered "Project Expenses" under the terms of the PF Agreement. In 2021, we received payments totaling $1.0 million from Lee's (HK) and no further amounts are due under the PF Agreement as of December 31, 2021.

With the termination of the PF Agreement in November 2020, we ceased enrollment in our phase 2b bridging study at the European Union, or EU, clinical sites and are transferring AEROSURF development activities to Lee's (HK) to be implemented under the terms of our Asia License Agreement. Since the 2018 acquisition of CVie Investments Limited and its wholly owned subsidiary CVie Therapeutics Limited, istaroxime has become our primary focus for investment and execution due to what we believe represents a greater potential value opportunity for us and our stockholders. Since completing our phase 2 study of lucinactant (KL4 surfactant) for patients with severe COVID-19 associated ARDS and lung injury in January 2022, in order to preserve resources for the highest priority programs, we have begun to reduce costs not already transferred to our licensee in Asia, Lee's (HK), under the terms of our Asia License Agreement. These costs include certain reductions in headcount dedicated to KL4 surfactant and the decommissioning of both our analytical and technical support laboratory, which previously conducted release testing of APIs and supportive research for our lyophilized and aerosolized KL4 surfactant, and our medical device development laboratory, which was previously used to conduct development activities and testing for our ADS technologies. To support the future development of our KL4 surfactant platform in markets outside of Asia, including the U.S., we are pursuing one or more licensing transactions.

Lyophilized KL4 Surfactant (Lung Injury and Other Studies)

We believe our lyophilized KL4 surfactant and ADS technologies may potentially support a product pipeline to address a range of serious respiratory conditions in children and adults. We have from time to time worked with independent investigators and pharmaceutical companies to conduct or assist with preclinical studies, some of which were funded under grants from National Institutes of Health, or NIH, and other government agencies, to assess the utility of using our KL4 surfactant, alone or in combination with other pharmaceutical compounds, to address various respiratory conditions.

Impact of COVID-19

The COVID-19 pandemic continues to evolve, and we continue to closely monitor its impact on our business and operations, including its continued impact on our clinical development plans and timelines, and financial condition. There has been intermittent impact of the pandemic in differing geographies, and there may be continued impact, particularly in light of the surge of new COVID-19 cases relating to new variants, such as the delta and omicron variants. As of the date of this Annual Report on Form 10-K, our operations, capital and financial resources and overall liquidity position and outlook have been impacted by COVID-19, primarily due to delays experienced in our operations, including in clinical study initiation and enrollment. The extended timelines have required us to expend more of our capital resources than planned to achieve our projected milestones. For example, our phase 2 study of istaroxime for early cardiogenic shock in heart failure patients experienced delays in trial initiation and enrollment in 2020 and 2021. The full extent, duration, or impact that the COVID-19 pandemic will have, directly or indirectly, on our financial condition and operations, including ongoing and planned clinical trials, will depend on future developments that are highly uncertain and cannot be accurately predicted. These potential future developments include new information that may emerge concerning the severity of the COVID-19 outbreak, the severity and transmissibility of new variants of the virus, information about any resurgences in one or more geographic locations where our current or intended clinical trial sites, our principal executive offices, research and development laboratories or manufacturing facilities are located, and the actions taken to contain it or treat its impact, which may include, among others, the timing and extent of government reopening activities and the economic impact on local, regional, national, and international markets. In addition, regional impact and responses to the COVID-19 pandemic have affected where a clinical trial could be executed and how various elements of the clinical trial are performed. Going forward, the pandemic could also impact how monitoring/auditing of clinical trial sites and data occur. The maintenance, or strategic re-implementation, of mitigating COVID-19 measures in one or more geographic locations where our clinical trial sites, principal executive offices, research and development laboratories or other facilities are located remains possible and if realized, we believe there could be further impact on the clinical development of our product candidates, which may include potential delays, halts or modifications to our ongoing and planned trials in 2022 and beyond.

Our Strategy

We intend to maximize the value of our product candidates and proprietary technologies. Our strategy to achieve this goal includes plans to:

- **Study istaroxime for early cardiogenic shock and, if the drug demonstrates adequate potential to raise blood pressure with an acceptable safety profile, pursue opportunity for an indication, which we believe may include a Breakthrough Therapy designation from the FDA, and if available, an expedited regulatory pathway to address this area of unmet medical need.** In March 2022, we completed a 60-patient phase 2a clinical trial in early cardiogenic shock, with topline data expected in April 2022;

- **Advance istaroxime for the treatment of AHF to a phase 3-ready position and potential partnering, collaboration or other strategic transaction.** We have begun start-up activities for an additional phase 2b clinical trial in approximately 300 patients and plan to execute the clinical trial after obtaining adequate funding;

- **Advance development of chronic and acute preclinical heart failure programs**. To create added value for our cardiovascular portfolio, we plan to advance oral (chronic) and intravenous (acute) SERCA2a activator product candidates through selected preclinical studies to demonstrate proof of concept; actively exploring potential licensing transactions, research partnership arrangements and other strategic opportunities;

- **Pursue non-dilutive funding and partnership support of a clinical trial meant to enhance the potential clinical positioning of rostafuroxin by examining its potential in the treatment resistant hypertension patient population.** Our primary objective for rostafuroxin is to identify out-licensing or other strategic arrangements for the completion of development and potential commercialization with one or more larger companies that have an interest in and/or operate in the very large and broad anti-hypertension market, and thereafter, to reinvest any proceeds to provide for our other core priority programs;

- **Continue to support Lee's (HK) in its development of the KL4 platform in Asia.** To support the future global development of our KL4 surfactant platform, including development in RDS via aerosolized AEROSURF and/or instillate delivery and/or in other potential applications such as acute lung injury, in markets outside of Asia, including the U.S., we are pursuing one or more licensing transactions; and

- **To enhance our product portfolio and leverage our depth of experience in late-stage clinical development and commercialization, we plan to pursue a focused business development agenda directed towards enhancing our current offerings and identifying additional product candidates that enhance our portfolio and provide more opportunity to grow value and diversify risk.** The strategic focus is on areas that fit our market focus (specialty critical, acute care and/or orphan designation), fit our scale for development and cost structure and leverage our therapeutic area and other competencies such as clinical-stage development.

Our Product Candidates

Istaroxime

Our lead cardiovascular product candidate is istaroxime, a novel, first-in-class, dual action investigational drug that we are developing to treat AHF and early cardiogenic shock. Istaroxime has been evaluated in two phase 2 clinical trials, the results of which suggest that istaroxime may improve cardiovascular physiological function as assessed by parameters of pump function, decreases in heart rate, increases in blood pressure and renal function (as measured by filtration rate) without adverse events such as arrhythmias or cardiac damage (as indicated by elevated troponin values). In August 2019, the FDA granted us Fast Track designation for istaroxime for the treatment of AHF.

AHF and Early Cardiogenic Shock Overview

Heart failure can result from structural or functional cardiac abnormalities. Heart failure is a chronic, progressive disease that commonly but episodically worsens to a point of critical decompensation, where cardiac output fails to meet the body's metabolic needs. The disease is characterized by inadequate pumping function of the heart that results in fluid accumulation manifesting as pulmonary congestion, peripheral edema and congestion in other parts of the body. Insufficient cardiac output can result in inadequate peripheral perfusion that increases the risk of other organ dysfunction such as renal failure. Chronic heart failure is commonly treated with multiple medications including diuretics, inhibitors of neurohumoral imbalances (angiotensin, renin, aldosterone, naturetic peptides) and beta blockers. Effective treatments for AHF in a hospital setting are lacking.

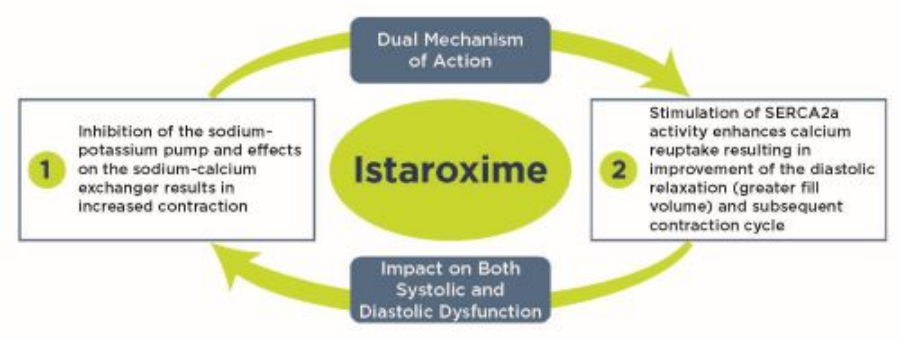
Clinical objectives for AHF patient management include: (i) relieve pulmonary congestion and general edema with intravenous diuretics, (ii) improve cardiac function and peripheral / organ perfusion, (iii) achieve a stable, fully compensated clinical state and, (iv) transition to oral, outpatient medicines (for chronic management of their heart failure).

Current approaches to acutely improve cardiac function are associated with unwanted effects including heart rhythm disturbances, increased heart rate and myocardial oxygen demand, decreased blood pressure, potential damage to the heart muscle, worsening renal function and even increases in mortality have been observed. In particular, patients with low systolic blood pressure, or SBP, and peripheral hypoperfusion are high risk, challenging patients and are also generally resistant to diuretic therapy and often discharged in a sub-optimal state.

Early cardiogenic shock is a severe presentation of heart failure characterized by very low blood pressure and risk for hypoperfusion to critical organs. It is associated with high mortality and morbidity and is not well treated with current therapies.

Method of Action

Istaroxime represents a novel approach to the treatment of AHF. It has a dual mechanism of action to improve cardiovascular physiology. First, it activates the SERCA2a calcium pump on the sarcoplasmic reticulum, or SR, leading to enhanced SR calcium uptake and a reduction in cytoplasmic calcium that is thought to improve myocardial relaxation. Second, it inhibits the sodium-potassium ATPase activity leading to improved myocardial contractility.



We believe that these mechanisms of action may result in improvement in cardiac function and perfusion to reduce congestion and edema and preserve other organ function while avoiding the side effects associated with other classes of heart failure therapies. Data from preclinical, phase 2a and phase 2b clinical studies performed to date suggest that istaroxime may improve cardiovascular physiology as assessed by parameters of pump function, decreases in PCWP, decreases in heart rate, increases in blood pressure without an increase in adverse events such as arrhythmias, cardiac damage (as indicated by elevated troponin values) or adverse impact on kidney function. We believe that these features of istaroxime, if approved, could potentially result in clinical improvement of patients' heart failure symptoms, reduce complications and improve other clinical outcomes when compared to current therapeutic regimens for AHF.

Clinical Development

Early Cardiogenic Shock

After assessing the regulatory landscape and data from the istaroxime phase 2 clinical program in AHF and discussions with our scientific advisors, we added to our istaroxime development program a study in early cardiogenic shock due to heart failure. We believe that istaroxime may fulfill an unmet medical need in early cardiogenic shock based on the profile observed in prior phase 2 clinical studies in AHF, in which istaroxime increased SBP, suggesting that istaroxime could potentially contribute to the clinical improvement of select patients in cardiogenic shock due to heart failure.

In the second half of 2020, we initiated a small study of istaroxime for the acute treatment of early cardiogenic shock in patients with more severe cases of heart failure, to evaluate the potential to improve blood pressure. This study is a phase 2 international randomized double-blind placebo-controlled study to assess the effect of istaroxime in patients with early cardiogenic shock due to heart failure. This study includes 60 patients (30 assigned to istaroxime and 30 assigned to placebo) receiving study drug infusion over 24 hours. The primary endpoint is the change in systolic blood pressure over six hours after initiating the infusion. Secondary endpoints will include characterization of blood pressure changes over 24 hours, the number of patients requiring rescue therapy (vasopressors, inotropes or mechanical devices), assessment of renal function and measures associated with safety and tolerability. The study will also evaluate the safety and side effect profile of istaroxime in this patient population. In March 2022, we completed enrollment of 60 patients and expect data to be available in April 2022. The global COVID-19 pandemic has had a disruptive effect on hospital resources (including in ICUs) where this study is being conducted. The COVID-19 pandemic has impacted the severity of illness of patients presenting with early cardiogenic shock and/or conditions that could lead to early cardiogenic shock. In addition, the geographic mix of patients can impact the outcome of a clinical trial, and with the global spread of COVID-19 occurring in waves, the mix of patients across countries has fluctuated. How these dynamics could potentially impact both timelines and outcomes is unknown.

AHF

Istaroxime has been evaluated in six clinical trials assessing various doses in 280 patients, including two phase 2 clinical trials. In a phase 2a randomized, double-blind, placebo-controlled, dose-escalation clinical trial, three doses of istaroxime were evaluated in a study of 120 hospitalized patients (approximately 30 patients per cohort) with AHF and reduced left ventricular ejection fraction. The three doses of istaroxime were administered intravenously over six hours. In this clinical trial, the primary endpoint of lowering of PCWP was significantly improved in all three doses relative to placebo, and certain secondary hemodynamic endpoints (increased systolic blood pressure and decreased heart rate) also improved. The main side effects were vomiting (7.9%) and pain at the infusion site (5.6%); one severe adverse event of ventricular tachycardia was observed. The favorable effects on PCWP, blood pressure and heart rate provided the basis for moving the program forward into a phase clinical 2b trial and for selecting the doses to study.

The primary endpoint of the istaroxime phase 2b clinical trial for AHF was a change from baseline to 24 hours after start of infusion (Day 1) in E/e' with istaroxime 0.5 or 1.0 µg/kg/min compared to placebo. The E/e' ratio is a marker of the function of the left ventricle, or LV, of the heart and was measured using doppler echocardiography read by a central laboratory. Secondary endpoints included change in other parameters of cardiac function, such as diastolic function, or E/A, stroke volume, or SVI, left ventricle ejection fraction, or LVEF, LV volumes, left atrial, or LA, area, interior vena cava, or IVC, diameter. A 24-hour infusion of istaroxime was associated with significant improvements in cardiac function, in both dosing groups, with a mean E/e' of -4.55 for the 0.5 µg/kg/min group and -3.16 for the 1.0 µg/kg/min group, compared with mean placebo E/e' ratios of -1.55 and -1.08, respectively. Twenty-four-hour infusions of istaroxime were also associated with substantial increases in stroke volume in both dosing groups, with a mean SVI value of 5.33 ml/beat/m^2 for the 0.5 µg/kg/min group and 5.49 ml/beat/m^2 for the 1.0 µg/kg/min group, compared with the mean placebo SVI of 1.65 ml/beat/m^2 and 3.18 ml/beat/m^2, respectively. Importantly, subjects also maintained or increased SBP, with a mean change in SBP of 2.82 mmHg for the 0.5 µg/kg/min group and 6.1 mmHg for the 1.0 µg/kg/min group, compared with the mean placebo SBP values of -2.47 mmHg and 2.7 mmHg, respectively. There were no signs of increased risk for arrhythmias or increased troponin levels (a marker of heart muscle damage) during or after istaroxime infusion. Additionally, blood pressure tended to increase, and heart rate decreased, during the infusion with istaroxime, which may have contributed to the short-term trend toward improvement in renal function. The findings were consistent with the physiologic improvements seen in the phase 2a study and the effects of istaroxime in AHF.

Istaroxime was generally well tolerated. Istaroxime did not appear to be associated with an increased risk for arrhythmias or increases in cardiac troponin T. The rate of cardiovascular-related adverse events was 23% for placebo, 10% for istaroxime low dose, and 18% for istaroxime high dose, with cardiac failure occurring in 3%, 5% and 8% of placebo, low dose and high dose patients, respectively. The cases of cardiac failure were reported by the investigator as "worsening of heart failure" symptoms that occurred approximately 10-14 days after study drug administration and were not considered to be drug related. The most common adverse drug reactions reported included pain at infusion site, generally associated with use of short catheters, and dose-related gastrointestinal adverse events in 5%, 10% and 38% of placebo, low dose and high dose patients, respectively. Serious adverse events included one cardiac death and one case of cardiogenic shock (in the same patient who died) in the istaroxime 1.0 µg/kg/min group, two cases of cardiac failure in the 0.5 µg/kg/min group, three cases of cardiac failure in the 1.0 µg/kg/min group, and one case of renal embolism in the 1.0 µg/kg/min group.

Based on feedback from the FDA in June 2019 and discussions with our scientific advisors, to advance istaroxime for the treatment of AHF potentially through the phase 2 clinical program and be in a phase 3-ready position, our strategy includes, subject to adequate resources, planning an additional phase 2 clinical trial that will enroll approximately 300 patients in approximately 60 clinical sites globally. This trial will focus on treating heart failure patients with low blood pressure, who also tend to be diuretic resistant, as a patient population that we believe could particularly benefit from the unique profile and potential ability of istaroxime to increase cardiac function and increase blood pressure while maintaining or improving renal function. This trial will also collect data on measures that may serve as primary endpoints in a phase 3 clinical trial, and will include an optimized dosing regimen, potentially extending the infusion time beyond 24 hours. We currently do not have sufficient capital to execute this clinical trial. We are exploring capital from public and private equity offerings and potential strategic opportunities to fund the initiation of this clinical trial, and plan to initiate the clinical trial after obtaining adequate funding. We plan to closely monitor the impact of the COVID-19 pandemic and its impact on hospital resources and resulting potential changes in regulatory timelines for conducting non-COVID-19-related clinical trials.

Manufacturing

Istaroxime is manufactured for us by an affiliate of Lee's (HK).

The API used in production of the drug product candidate is manufactured by ScinoPharm Taiwan, Ltd.

We contracted with Clinigen for the receipt, labeling, packaging and distribution of drug and materials to support the istaroxime phase 2 clinical trial in early cardiogenic shock.

Rostafuroxin

Rostafuroxin is a novel investigational drug product candidate being developed for the treatment of hypertension in patients with a specific genetic profile, which is found in approximately 20% - 25% of the adult hypertensive population.

Hypertension Overview

According to the CDC, patients with high blood pressure have a greater risk for heart disease and stroke, which are leading causes of death in the U.S. Nearly half of adults in the U.S. (108 million, or 45%) have hypertension defined as a systolic blood pressure ≥ 130 mm Hg or a diastolic blood pressure ≥ 80 mm Hg or are taking medication for hypertension. In 2018, nearly half a million deaths in the U.S. included hypertension as a primary or contributing cause. Only about 1 in 4 adults (24%) with hypertension have their condition under control. Patients often have persistent hypertension despite being on multiple therapies. Ethnicity and genetic makeup are known to impact the response to anti-hypertensive treatments, and uncontrolled hypertension has been associated with certain genetic makeups. Given the size of the market and the prevalence of unmet medical needs, major pharmaceutical companies have maintained hypertension as a key area of focus and continue to seek new drugs to compete in markets they have established with previous anti-hypertensive therapies. We are currently engaged in a process to test the industry's interest in investing in new drugs in this market, and plan to pursue potential licensing transactions and/or other strategic opportunities with a company that has interest in and/or operates in the anti-hypertension market.

Method of Action

Rostafuroxin is designed to be a selective antagonist of adducin polymorphisms and endogenous ouabain, both known triggers of hypertension, and creates functional effects by enhancing renal tubular sodium reabsorption and increasing vascular tone.

Clinical Development

Rostafuroxin has been studied in three phase 2 clinical trials assessing reduction in blood pressure in a hypertensive population selected in accordance with a specified genetic profile. A phase 2b clinical trial was conducted as a two-part study with the first part conducted in Italy with Caucasian patients and the second part conducted in Taiwan with ethnic Chinese patients. The efficacy results in Italy were positive in both this trial and in an earlier phase 2a clinical trial; however, the blood pressure response in Chinese patients in the second part of the phase 2b study was minimal.

Rostafuroxin has demonstrated efficacy in Caucasian patients in treatment naïve hypertension in a phase 2b trial. During the second quarter, we concluded an initial process to test the industry's interest in investing in our product candidate. We currently have not been able to secure a licensing transaction or other strategic opportunity. As a result, we recorded an impairment of the related intangible asset (*see*, Note 4 – Accounting Policies and Recent Accounting Pronouncements – Goodwill and Intangible Assets). Based on feedback received from potential licensing partners, we have determined that there is a need for an additional phase 2 clinical trial to demonstrate efficacy in non-Caucasian patients in treatment resistant hypertension. We are continuing to pursue licensing arrangements and/or other strategic partnerships for rostafuroxin. We do not intend to conduct the additional phase 2 clinical trial without securing such an arrangement or partnership.

Manufacturing

The drug product candidate for rostafuroxin is manufactured by an affiliate of Lee's (HK).

The API used in the production of the drug product candidate is manufactured by SciAnda (Changshu) Pharmaceutical, Ltd.

Preclinical Heart Failure Product Candidates

We are pursuing early exploratory research to assess our preclinical follow-on oral and intravenous SERCA2a activator heart failure compounds. To advance these product candidates, we are actively exploring potential licensing transactions, research partnership arrangements or other strategic opportunities.

KL4 Surfactant

We believe our KL4 surfactant and ADS technologies may potentially support a product pipeline to address a range of serious respiratory conditions in children and adults. Since completing our phase 2 study of lucinactant (KL4 surfactant) for patients with severe COVID-19 associated ARDS and lung injury in January 2022, in order to preserve resources for the highest priority programs, we have begun to reduce costs not already transferred to our licensee in Asia, Lee's (HK), under the terms of our Asia License Agreement. These costs include certain reductions in headcount dedicated to KL4 surfactant and the decommissioning of both our analytical and technical support laboratory, which previously conducted release testing of APIs and supportive research for our lyophilized and aerosolized KL4 surfactant, and our medical device development laboratory, which was previously used to conduct development activities and testing for our ADS technologies. To support the future development of our KL4 surfactant platform in markets outside of Asia, including the U.S., we are pursuing one or more licensing transactions.

COVID-19 related Lung Injury Overview

Patients with COVID-19 pneumonia may progress to ARDS and require supplemental oxygen and mechanical ventilation. ARDS has no approved therapies and is associated with significant morbidity, mortality and healthcare resource utilization. The COVID-19 virus infects via angiotensin-converting enzyme 2 receptor, or ACE2, on surfactant producing cells in the lung. This impairs surfactant production, resulting in poor gas exchange, decreased lung compliance, and increased likelihood of needing mechanical ventilation. Pre-clinical and clinical evidence shows surfactant replacement therapy has the potential to improve lung function, oxygenation, lung compliance and decrease pulmonary inflammation. These beneficial effects could lead to potential clinical improvements such as decreased need for mechanical ventilation, decreased time on ventilator (freeing the devices for other patients) and possibly mortality.

RDS Overview

Our KL4 surfactant can be lyophilized (freeze-dried) and reconstituted to a liquid just prior to administration. We have in the past considered potential development pathways to secure marketing approval for lyophilized KL4 surfactant as an intratracheal instillate for the treatment and/or prevention of RDS in premature infants who, because they are unable to breathe on their own or other reason, are not candidates for AEROSURF. Lyophilized KL4 surfactant is the drug product component of AEROSURF and a lyophilized (freeze-dried) dosage form of the liquid KL4 surfactant intratracheal instillate, SURFAXIN®, that was approved by the FDA in 2012, but the SURFAXIN drug product was withdrawn from the market by us voluntarily in 2015 to focus our resources on the development of aerosolized KL4 surfactant for respiratory diseases, beginning with AEROSURF. We have demonstrated in laboratory experiments that our lyophilized KL4 surfactant retains many of the key attributes and characteristics of SURFAXIN. We expect that Lee's (HK) will continue to pursue approval of lyophilized KL4 surfactant in Asia pursuant to the Asia License Agreement.

Clinical Development

COVID-19 related Lung Injury

In January 2022, we completed enrollment of 20 patients in our study of lucinactant (KL4 surfactant) for patients with severe COVID-19 associated ARDS and lung injury. The phase 2 trial was designed to assess feasibility, safety, and tolerability of administration of reconstituted lyophilized lucinactant in these critically ill patients. The multicenter, single-arm study enrolled 20 critically ill patients who were intubated and on mechanical ventilation due to severe COVID-19 associated ARDS. Patients received lucinactant as a liquid via the endotracheal tube assessing safety and tolerability of the administration procedure and of the drug. Oxygenation and other physiological responses were also measured. Study sites were in the U.S. and Argentina.

The study demonstrated that intratracheal administration of reconstituted lyophilized lucinactant was generally safe and well tolerated. Lucinactant was safely administered to critically ill, mechanically ventilated patients with severe COVID-19 associated ARDS. Oxygenation and other physiological parameters were stable to improved after dosing, supporting the feasibility of this treatment approach to develop a potential treatment for critically ill patients with ARDS due to COVID-19 or other causes.

AEROSURF

Overview

AEROSURF® (lucinactant for inhalation) is an investigational drug/medical device combination product candidate to improve the management of RDS in premature infants who may not have fully developed natural lung surfactant and may require surfactant therapy to sustain life. AEROSURF is designed to deliver aerosolized KL4 surfactant noninvasively using our proprietary ADS technology and potentially may meaningfully reduce the use of invasive endotracheal intubation and mechanical ventilation.

Clinical Development

On March 18, 2020, we entered into the Term Sheet with Lee's (HK) pursuant to which Lee's (HK) agreed to provide financing to fund the development of AEROSURF for the period April 1, 2020 through September 30, 2020 and make payments of up to $3.9 million (which was reduced to $2.8 million under specified circumstances) prior to September 1, 2020. In August 2020, we entered into the PF Agreement with Lee's (HK), formalizing the terms of the Term Sheet, and under which we received payments totaling $2.8 million through October 2020. Pursuant to the PF Agreement, Lee's (HK) agreed to pay additional amounts to be set forth in an updated development budget to be agreed between the parties by September 1, 2020 and updated every six months thereafter, to fund the continued development of AEROSURF and to be paid with the payment schedule to be set forth in each updated development budget. In partial satisfaction of our obligations under the PF Agreement, we agreed to pay Lee's (HK) 50% of any Commercialization Net Revenues (as defined in the PF Agreement) up to an amount that is equal to 125% of the Project Expenses (as defined in the PF Agreement) funded by Lee's (HK). On November 12, 2020, Lee's (HK) provided notice of termination of additional funding under the PF Agreement, and we and Lee's (HK) revised our plans for the continued development of AEROSURF. Lee's (HK) agreed to continue the development of AEROSURF in Asia at its own cost. Lee's (HK) agreed to fund an additional $1.0 million to us in 2021 for certain transition and analytical services to be provided by us with respect to the development of AEROSURF, which will be considered "Project Expenses" under the terms of the PF Agreement. In 2021, we received payments totaling $1.0 million from Lee's (HK) and no further amounts are due under the PF Agreement as of December 31, 2021.

Since the 2018 acquisition of CVie Investments Limited and its wholly owned subsidiary CVie Therapeutics Limited, istaroxime has become our primary focus for investment and execution due to what we believe represents a greater potential value opportunity for us and our stockholders. Since completing our phase 2 study of lucinactant (KL4 surfactant) for patients with severe COVID-19 associated ARDS and lung injury in January 2022, in order to preserve resources for the highest priority programs, we have begun to reduce costs not already transferred to our licensee in Asia, Lee's (HK), under the terms of our Asia License Agreement. These costs include certain reductions in headcount dedicated to KL4 surfactant and the decommissioning of both our analytical and technical support laboratory, which previously conducted release testing of APIs and supportive research for our lyophilized and aerosolized KL4 surfactant, and our medical device development laboratory, which was previously used to conduct development activities and testing for our ADS technologies. To support the future development of our KL4 surfactant platform in markets outside of Asia, including the U.S., we are pursuing one or more licensing transactions.

Manufacturing

KL4 surfactant is comprised of four APIs, which were previously supplied to us by sole-source suppliers under now expired supply agreements or purchase orders.

Our lyophilized KL4 surfactant was manufactured for us by Pharma Services Group, Patheon, part of Thermo Fisher Scientific, or Patheon. In March 2022, we provided notice to Patheon of our plans to wind-down our Master Services Agreement dated as of October 24, 2013 for the manufacture of lyophilized KL4 surfactant. Manufacturing of the KL4 drug product in both liquid and lyophilized forms is in the process of being transferred to our licensee in Asia, Lee's (HK), under the terms of our Asia License Agreement.

With respect to our ADS, we are currently undertaking a technology transfer of our device manufacturing process from Battelle Memorial Institute, or Battelle, to Mack Molding Company, or Mack, an FDA-registered medical device manufacturer. We currently have a Memorandum of Understanding with Mack to cover this transfer. Upon completion of the technology transfer to Mack, we expect that the manufacturing of the ADS will be transferred to our licensee in Asia, Lee's (HK), under the terms of our Asia License Agreement.

Material Licenses and Collaborations

Lee's Pharmaceutical (HK) Ltd. Asia License Agreement

We are party to an Asia License Agreement with Lee's (HK), an affiliate of Lee's Holdings. Under the Asia License Agreement, we granted to Lee's (HK) an exclusive license with a right to sublicense (i) to develop, manufacture and commercialize our KL4 surfactant products, including SURFAXIN, which was approved by the FDA in 2012 for RDS in premature infants, SURFAXIN LS™, the lyophilized dosage form of SURFAXIN, and AEROSURF, including the ADS, and (ii) to register and manufacture SURFAXIN and SURFAXIN LS for use in the licensed territory, which includes China, Japan, Hong Kong, Thailand, Taiwan and 12 other countries. Under the Asia License Agreement, Lee's (HK) made an upfront payment to us of $1.0 million. We also may receive up to $35.8 million in potential clinical, regulatory and commercial milestone payments and will share in any sublicense income Lee's (HK) may receive at a rate equal to low double digits. In addition, Lee's (HK) is responsible for all costs and expenses in and for the licensed territory related to development activities, including a planned AEROSURF phase 3 clinical program, regulatory activities, and commercialization activities.

We will be eligible to receive tiered royalties based on a percent of Net Sales (as defined in the Asia License Agreement), depending on the product, in the range of high single to low-to-mid double-digit percentages. Royalties are payable on a country-by-country basis until the latest of (i) the expiration of the last valid patent claim covering the product in the country of sale, (ii) the expiration or revocation of any applicable regulatory exclusivity in the country of sale, and (iii) ten years after the first commercial sale in the country of sale. Thereafter, in consideration of licensed rights other than patent rights, royalties shall continue for the commercial life of each product and, for the initial three years, shall be in the range of low-to- mid single digits. In addition, in the event that one or more generic products are introduced, the royalty rates will be reduced, subject to certain minimums if we are subject to continuing obligations at the time to pay royalties under our in-license agreements.

Under the Asia License Agreement, Lee's (HK) is responsible for all activities related to development, regulatory approval and commercialization of KL4 surfactant and drug/medical device combination products in the licensed territory. Lee's (HK) will hold the product licenses for all non-aerosolized products in the licensed territory and will seek regulatory approval initially for SURFAXIN and SURFAXIN LS for RDS. We will hold the product license in the licensed territory (except where prohibited by law) for all aerosolized products and will designate Lee's (HK) our exclusive agent and representative to develop and register AEROSURF and other aerosolized products in our name and on our behalf. Lee's (HK) also has agreed that, except as provided in the Asia License Agreement, for a period of ten (10) years beginning with the later of the first commercial sale of the first aerosolized product and the first commercial sale of the first non-aerosolized product in China, it will not develop, register, manufacture, or commercialize any product for the prevention and/or treatment of RDS in premature infants or other diseases and conditions in humans, in either case, that administers, utilizes or contains pulmonary surfactant without our prior written consent.

The term of the Asia License Agreement will continue on a country-by-country basis for the commercial life of the products. Either party may terminate the Asia License Agreement in the event of bankruptcy or a material breach of the Asia License Agreement by the other party that remains uncured for a period of sixty (60) days. In addition, either party may terminate the Asia License Agreement in its entirety or with respect to any individual product or country if a regulatory authority terminates, suspends or discontinues development of a product and such termination, suspension or discontinuance persists for a period in excess of eighteen (18) months. Upon termination of the Asia License Agreement in its entirety or with respect to a particular product or country, generally all related rights and licenses granted to Lee's (HK) will terminate, all rights under our technology will revert to us, and Lee's (HK) will cease all use of our technology.

Universita degli Studi di Milano-Bicocca Collaboration Agreement

In April 2015, our subsidiary, CVie Therapeutics Limited, or CVie Therapeutics, entered into an Agreement for Scientific Collaboration, or the 2015 Agreement, with the Universita degli Studi di Milano-Bicocca, or Bicocca, in Milan, Italy, focused on defining the role of SERCA2a and phospholamban, or PLN, in modulating cardiac contraction, and discovering new small molecules to modulate SERCA2a activity or new drugs for treating chronic and acute human heart failure. The initial term of the 2015 Agreement, which was three years, was extended for approximately an additional year, with an option for further renewal. In June 2019, we entered into a new Agreement for Scientific Collaboration with Bicocca, or the 2019 Agreement, focused on continuing the studies under the 2015 Agreement. The 2019 Agreement supersedes and replaces all prior agreements with Bicocca.

Under the 2019 Agreement, we provided funds aggregating € 0.16 million (approximately $0.178 million) to extend our use of Bicocca laboratories and to fund research conducted pursuant to the collaboration. (Under the 2015 Agreement, Bicocca had given us exclusive use of a research laboratory for the collaboration work, and nonexclusive access to a physiology laboratory within the university.) Under the 2019 Agreement, any results obtained from the collaboration are jointly owned by the parties. However, Bicocca has agreed to assign to us its interest in patent applications and patents covering any new SERCA2a activator compounds and diagnostic products suitable for further clinical development. We have agreed to pay Bicocca (corresponding to stage of development): (i) € 0.1 million (approximately $0.11 million) for new SERCA2a activator compounds developed up to phase 1 studies in humans upon the completion and availability of the proof of concept of biological efficacy of new compounds on modulating the SERCA2a activity in cell-free systems, or its functional counterpart in cardiac myocytes and (ii) € 1.5 million (approximately $1.7 million) upon obtaining marketing authorization in the U.S., EU, or China of new compounds with the corresponding companion diagnostic assay. We have also agreed to pay royalties on products generated from the collaboration in the range of a fraction of a single digit to a low single digit percent of net sales for any products sold in any country for a period of ten years from the date of the first commercial sale or until the expiry of patent(s) covering the products.

On March 19, 2021, we entered into an Agreement for Scientific Collaboration, or the New SERCA2a Agreement, with Bicocca, which extends our collaboration. The New SERCA2a Agreement amends and restates the recently expired terms of the prior collaboration agreement. Under the New SERCA2a Agreement, we will provide Bicocca with approximately € 0.2 million (approximately $0.2 million) for research activities and to cover laboratory space and operation costs. Results obtained from the collaboration will be jointly owned by the parties. However, Bicocca will assign to us its interest in patent applications and patents covering any new SERCA2a compounds and diagnostic products suitable for further clinical development. We have agreed to pay Bicocca (corresponding to stage of development): (i) € 25,000 for execution of an assignment to us of Bicocca's interest in the patent at issue, (ii) € 75,000 for new SERCA2a compounds developed up to phase 1 studies in humans upon the completion and availability of the proof of concept of biological efficacy of new compounds on modulating the SERCA2a activity in cell-free systems, or its functional counterpart in isolated cells and (iii) € 1.5 million upon obtaining marketing authorization in the U.S., EU, or China of new compounds with the corresponding companion diagnostic assay. We have also agreed to pay royalties on products generated from the collaboration in the range of a fraction of a single digit to a low single digit percent of net sales for any products sold in any country for a period of ten years from the date of the first commercial sale or until the expiry of patent(s) covering the products.

Philip Morris License Agreements

In 2008, we entered into an Amended and Restated License Agreement with Philip Morris USA, Inc., or PMUSA, with respect to the U.S., or the U.S. License Agreement, and, as PMUSA had assigned its ex-U.S. rights to Philip Morris Products S.A., or PMPSA, effective on the same date and on substantially the same terms and conditions, we entered into a license agreement with PMPSA with respect to rights outside of the U.S., which we refer to, together with the U.S. License Agreement, as the PM License Agreements. Under the PM License Agreements, we have worldwide exclusive rights to the PMUSA and PMPSA proprietary capillary aerosol technology, which is a key component of our ADS, for use in a drug/device combination product with pulmonary surfactants (alone or in combination with other pharmaceutical compounds) for all respiratory diseases and conditions. In addition, under the U.S. License Agreement, our license to use the capillary aerosol technology includes certain non-surfactant drugs to treat certain designated pediatric and adult respiratory indications in hospitals and other health care institutions. *See also*, "– Patents and Proprietary Rights – Aerosol Delivery System (ADS) Patent Rights."

Under the PM License Agreements, we are obligated to pay royalties at a rate equal to a low single-digit percent of sales of products sold in the Exclusive Field (as defined in the PM License Agreements) in the territories. In connection with exclusive undertakings of PMUSA and PMPSA not to exploit the aerosol technology for all licensed uses, we are obligated to pay royalties on all product sales, including sales of certain aerosol devices that are not based on the licensed aerosol technology; provided, however, that no royalties are payable to the extent that we exercise our right to terminate the license with respect to a specific indication. While there is no legal obligation under the PM License Agreements to make minimum royalty payments, in the event we do not make quarterly minimum royalty payments, PMUSA and PMPSA can terminate the PM License Agreements. In making such payments, we are entitled to reduce future quarterly royalties above the quarterly minimums in the amount of the true-up payments we make to satisfy minimum royalties for prior quarters. Our license rights extend to innovations to the aerosol technology that are made under the PM License Agreements.

In addition to customary termination provisions for breach of the agreements, we may terminate the PM License Agreements, in whole or in part, upon advance written notice to the licensor. In addition, either party to each PM License Agreement may terminate upon a material breach by the other party (subject to a specified cure period). PMUSA and PMPSA may also terminate the PM License Agreements in the event that we fail to make certain minimum royalty payments. Our license under each PM License Agreement, unless terminated earlier, will expire as to each licensed product, on a country-by-country basis, upon the latest to occur of: the date on which the sale of such licensed product ceases to be covered by a valid patent claim in such country; the date a generic form of the product is introduced in such country; or the tenth anniversary of the first commercial sale of such licensed product.

Battelle Collaboration Agreement

In October 2014, we entered into a Collaboration Agreement with Battelle, or, as amended, the Battelle Collaboration Agreement, for the development of our new ADS for use in our phase 3 program. We had previously worked with Battelle, which has expertise in developing and integrating aerosol devices using innovative and advanced technologies, in connection with development of our phase 2 ADS used in the AEROSURF phase 2b clinical trial. Under the Battelle Collaboration Agreement, we and Battelle shared the costs of development for a three-stage development plan that included planning, executing the project plan and testing and completing verification and documentation of a new phase 3 ADS, putting us in a position to manufacture a new phase 3 ADS for use in the remaining AEROSURF development activities, including a potential phase 3 clinical program, and, if approved, initial commercial activities. We retained final decision-making authority over all matters related to the design, registration, manufacture, packaging, marketing, distribution and sale of the phase 3 ADS. We and Battelle shared the costs of the project plan equally. Battelle agreed to bear the cost of any cost overruns associated with the project plan and we agreed to bear the cost of any increase in cost resulting from changes in the scope of the product requirements. We also agreed that, if Battelle successfully completed the project plan in a timely manner, we would pay Battelle royalties equal to a low single-digit percentage of the worldwide net sales and license royalties on sales of AEROSURF for the treatment of RDS in premature infants, up to an initial aggregate limit of $25.0 million, which under a payment restructuring agreement (discussed below), was increased to $35.0 million. The Battelle Collaboration Agreement will end at the time we fulfill our payment obligations to Battelle, unless sooner terminated by a party as provided therein.

Laboratorios del Dr. Esteve, S.A. Strategic Alliance

We have a strategic alliance with Laboratorios del Dr. Esteve, S.A., or Esteve, for the development, marketing and sales of a portfolio of potential KL4 surfactant products in Andorra, Greece, Italy, Portugal, and Spain, or, collectively, the Territory. Under the alliance, Esteve will pay us a transfer price on sales of our KL4 surfactant products. We are responsible for the manufacture and supply of all covered products and Esteve will be responsible for all sales and marketing in the Territory. Esteve is obligated to make stipulated cash payments to us upon our achievement of certain milestones, primarily upon receipt of marketing regulatory approvals for the covered products. In addition, Esteve has agreed to contribute to phase 3 clinical trials for the covered products by conducting and funding development performed in the Territory. As part of a 2004 restructuring, Esteve returned certain countries to us, referred to as the Former Esteve Territories, and we agreed to pay Esteve 10% of any cash up front and milestone fees (up to a maximum aggregate of $20.0 million) that we receive in connection with any strategic collaborations for the development and/or commercialization of certain of our KL4 surfactant products in the Former Esteve Territories. In addition, with respect to our aerosolized KL4 surfactant, Esteve will pay us $0.5 million upon the initial filing for regulatory approval with the European Medicines Agency, or EMA, and $0.5 million upon receipt of regulatory approval. Esteve will also contribute up to $3 million to support a phase 3 clinical trial in the Territory. The alliance will terminate as to each covered product, on a country-by-country basis, upon the latest to occur of: the expiration of the last patent claim related to a covered product in such country; the first commercial sale in such country of the first-to-appear generic formulation of the covered product, and the tenth anniversary of the first sale of the covered product in such country. In addition to customary termination provisions for breach of the agreement by a party, the alliance agreement may be terminated by Esteve on 60 days' prior written notice, up to the date of receipt of the first marketing regulatory approval, or, on up to six months' written notice, if the first marketing regulatory approval has issued. We may terminate the alliance agreement in the event that Esteve acquires a competitive product (as defined in the agreement).

Johnson & Johnson License Agreement

Our precision-engineered KL4 surfactant technology was invented at The Scripps Research Institute, or Scripps, and was exclusively licensed to and further developed by Johnson & Johnson, or J&J. Pursuant to a license agreement, dated October 28, 1996, with J&J and its wholly owned subsidiary, Ortho Pharmaceutical Corporation, or the J&J license, we obtained an exclusive, worldwide license and sublicense to a series of over 30 patents and patent filings (worldwide), or the J&J Patents. All J&J Patents have expired. Under the license agreement, we are obligated to pay the licensors fees of up to $3.0 million in the aggregate upon our achievement of certain milestones, primarily upon receipt of marketing regulatory approvals for certain designated products. We have made milestone payments totaling $1.0 million to date. In addition, the agreement provides that we are required to pay royalties at different rates based on the type of revenue and country, in amounts in the range of a high single-digit percent of net sales (as defined in the license agreement) of licensed products sold by us or sublicensees, or, if greater, a percentage of royalty income from sublicensees in the low double digits. The license agreement provides that the license will expire, on a country-by-country basis, upon the payment of royalties for all licensed products for ten years beginning on the date of the first commercial sale of the first licensed product in such country. Thereafter, the license agreement provides that royalties shall be paid in respect of a licensed product until the expiration of the last licensed patent containing a valid claim covering the licensed product in such country. For countries in the EU in which royalties are paid only by virtue of licensed know-how, royalties shall be payable commencing from the date of first commercial sale of the first licensed product in such country and ending on the earlier of (i) the date on which the licensed know-how becomes public or (ii) the tenth anniversary of the first commercial sale of the first licensed product in any country of the EU. In addition to customary termination provisions for breach of the agreement by a party, we may terminate the agreement, as to countries other than the U.S. and Western Europe territories (as defined in the agreement), on a country-by-country basis, on six months' prior written notice; and as to the entire agreement, on 60 days' prior written notice.

Intellectual Property

We continue to invest in maintaining and enforcing our potential competitive position through a number of means: (i) by protecting our exclusive rights in our cardiovascular agents including istaroxime, rostafuroxin and SERCA2a activators, (ii) by protecting our exclusive rights in our lyophilized KL4 surfactant, ADS and aerosol-conducting airway connector technologies through patents that we own or exclusively license, (iii) by seeking regulatory exclusivities, including potential Orphan Drug and new drug product exclusivities, and (iv) through protecting our trade secrets and proprietary methodologies that support our manufacturing and analytical processes.

Patents and Proprietary Rights

In addition to the inventions covered by the patents and patent applications described in this Annual Report on Form 10-K, we have been active in identifying and seeking to identify new inventions eligible for patent protection. We have filed and plan to file patent and provisional patent applications to protect our innovations relating to our current and potential future product candidates, including for composition of matter, new dosage forms, formulations, methods of manufacture, methods of use and related processes. We intend to file for patent protection for select inventions, in such markets that we deem material to our patent strategy, as well as for other new inventions that we may identify.

Our Patents and Patent Applications Related to Rostafuroxin, Istaroxime and SERCA2a Activators

We hold a patent portfolio of six patent families that include patents and patent applications directed to compounds, pharmaceutical formulations, methods of manufacturing, methods of delivery, and/or treatment methods using istaroxime, rostafuroxin, their metabolites and/or derivatives, as well as SERCA2a activators, for the treatment of cardiovascular diseases and related conditions. We plan to continue these patent activities and focus on new follow-on compounds, dosage forms, formulations, and treatment methods related to AHF and persistent hypertension. To benefit from potential non-patent exclusivity within the U.S., we believe that we may qualify istaroxime as a new chemical entity entitled to market exclusivity for a period of years. See the section titled "- Government Regulation - Drug Products - The Hatch-Waxman Act - Market Exclusivity."

- ***Istaroxime-Related Patents and Patent Applications***

  In November 2019, we filed an international patent application PCT/US2019/060961, directed to methods of treating AHF through an extended istaroxime dosing regimen, as well as to metabolites of istaroxime having SERCA2a stimulating activity. The international application entered the national phase in China on December 31, 2019 (Application No. 201980003356.1), and in the following PCT contracting states/regions in September and October of 2021: Australia, Brazil, Canada, European Patent Office, Israel, Hong Kong (extended from China), Japan, Mexico, Republic of Korea, and Singapore. This patent family will expire on or about November 12, 2039.

  An expedited U.S. patent application based on PCT/US2019/060961 was filed with the United States Patent and Trademark Office, or USPTO, on April 16, 2020, and issued as U.S. Patent No. 11197869 on December 14, 2021. The U.S. Patent, titled: "Istaroxime-Containing Intravenous Formulation for the Treatment of Acute Heart Failure (AHF)," covers longer infusion durations of istaroxime for improved outcomes in the treatment of acute heart failure. In particular, the patent refers to results in improvement in at least one echocardiographic indicator of diastolic function, which we attribute to the SERCA2a mechanism of action of istaroxime and its metabolites. A follow-on U.S. continuation patent application has been filed and is pending before the USPTO.

- ***New Compounds for Treatment of Heart Failure and Related Conditions***

  Two patent application families have resulted from research under the 2019 Agreement with Bicocca. Pursuant to that agreement, those patent families have been or are obligated to be assigned to CVie (or to us).

  In July 2018, the parties to the 2019 Agreement filed European Application No. EP18185753.3, directed to 17ß-heterocyclyl-digitalis like compounds and their use for the treatment of heart failure and related conditions. International application PCT/EP2019/069283, based on the European application, was filed in July 2019. National applications based on PCT/EP2019/069283 were filed in January and February 2021 in Australia, Brazil, Canada, China (extended into Hong Kong), Israel, Japan, Mexico, Republic of Korea, Singapore, and the U.S. Patents granted on this family of applications will expire on or about July 17, 2039.

  In October 2019, the parties to the 2019 Agreement filed European Application No. 19202257.2, directed to androstane derivatives with activity as pure or predominantly pure stimulators of SERCA2a for the treatment of heart failure and related conditions. International application PCT/EP2020/078253 and Taiwan Application No. 109134997, both based on the European application, were filed in October 2020. Patents granted on this family of applications will expire on or about October 8, 2040.

- ***Rostafuroxin-Related Patents***

  In June 2008, international patent application PCT/EP2008/056928 was filed, directed to rostafuroxin derivatives useful for the prevention or treatment of restenosis after angioplasty or endarterectomy, as well as diseases resulting from organ fibrosis. The international application entered into the national phase in the U.S., European Patent Office, or EPO, and several other foreign jurisdictions. In this patent family, multiple foreign counterparts are pending or granted. U.S. Patent Application No. 12/602,827 was abandoned following an unsuccessful appeal of a decision of the U.S. Patent Office examiner. European Patent No. 2160190B1 will expire on June 4, 2028.

  In March 2010, international patent application PCT/EP2010/053571 was filed, directed to rostafuroxin derivatives for the treatment of proteinuria, glomerulosclerosis, and renal failure. The international patent application entered into the national phase in the EPO (EP10709529.1, now European Patent No. 2411015B1), U.S., and multiple other foreign nations. U.S. Patent Application No. 13/258,728 was abandoned on June 2, 2016 in favor of child application U.S. 14/931,083, now U.S. Patent No. 9,868,757. U.S. Patent No. 9,868,757 and European Patent No. 2411015B1 will expire on March 18, 2030.

  In October 2010, international patent application PCT/EP2010/065589 was filed, covering methods of rostafuroxin administration for the treatment or prevention of cardiovascular conditions in individuals with various single nucleotide polymorphisms, or SNPs, associated with improved therapeutic response to rostafuroxin administration. The international patent application entered into the national phase in the EPO (EP10807525.0, now European Patent No. 2490694B1), U.S. (U.S. 13/502,518, now U.S. Patent No. 9,408,854), and multiple other foreign nations. U.S. Patent No. 9,408,854 and European Patent No. 2490694B1 will expire on October 18, 2030.

Our KL4 -Related Patents and Patent Rights

We have been active in seeking patent protection for our innovations relating to new dosage forms, formulations and methods of manufacturing and delivering synthetic peptide containing pulmonary surfactants. Our patent activities have focused particularly on improved dosage forms and delivery of aerosolized pulmonary surfactant.

In January 2006, we filed U.S. and international patent applications (U.S. 11/326,885 which is now U.S. Patent No. 7,541,331 issued on June 2, 2009 and PCT/US06/000308), directed to a surfactant treatment regimen for BPD. U.S. Patent No. 7,541,331 will expire on January 6, 2026.

In September 2007, we filed U.S. and international patent applications (U.S. 11/901,866 which is now U.S. Patent No. 8,221,772 and PCT US/2007/020260), directed to surfactant compositions and methods of promoting mucus clearance and treating pulmonary disorders such as cystic fibrosis. U.S. Patent No. 8,221,772 will expire on September 19, 2027.

In March 2013, we filed international patent applications (PCT/US13/34364 and PCT/US13/34464, which entered national phase and commenced expedited examination in the U.S. and EPO) directed to lyophilized pulmonary surfactant and methods of manufacture. In this patent family, two U.S. Patents Nos. 8,748,396 and 8,748,397, were issued on June 10, 2014, European patent 2723323B1 granted on September 23, 2015, U.S. Patent No. 9,554,999, issued on January 31, 2017 and multiple foreign counterparts are pending or granted. U.S. Patents Nos. 8,748,396; 8,748,397 and 9,554,999 and European Patent No. 2723323B1 will expire on March 28, 2033.

Aerosol Delivery System (ADS) Patent Rights

Pursuant to the PM Licenses Agreements, we have worldwide exclusive rights to the proprietary capillary aerosol technology incorporated into the ADS for use in a drug/device combination product. The ADS is the medical device component of our AEROSURF product candidate. We completed design verification of the new ADS for use in the remaining AEROSURF development activities, including a phase 2b bridging study to be conducted in China, potentially a phase 3 clinical program and, if approved, initial commercial activities.

Our ADS technology and our new ADS are protected by a portfolio of issued patents and pending patent applications covering various components of the system. While certain of the earlier patents on the technology have expired, there remain over 150 in-force patents worldwide that protect, among other things, core elements of the ADS technology and the new ADS. These patents and applications will expire on dates ranging from 2021 to 2039. As an illustrative example, important components of our new ADS technology are covered by a patent family represented by US Patent No. 9,713,687, expiring on February 10, 2035, and European Patent No. 2887984B1, expiring on August 21, 2033. In addition, several key components of our new ADS are covered by recently issued U.S. Patent No. 10,874,818, which expires on January 22, 2039.

Aerosol-Conducting Airway Connector Technology Patents and Patent Rights

In March 2009, we filed an international patent application (PCT US/2009/037409) directed to aerosol-conducting airway connectors and improvements of an ADS using AFECTAIR®. The claims of this application are directed to a novel ventilation circuit adaptor (an aerosol-conducting airway connector) and related aerosol circuitry that are intended to (i) increase the efficiency of aerosol delivery to the patient by allowing more efficient delivery of aerosols to the patient, and (ii) reduce drug compound dilution and wastage and result in more precise aerosol dosing. In this patent family, U.S. Patent No. 8,701,658 was issued on April 22, 2014, European patent No. 2265309 was granted on December 16, 2015, U.S. Patent No. 9,352,114 was issued on May 31, 2016, U.S. Patent No. 9,592,361 was issued on March 14, 2017 and several foreign patents have issued during 2011 through 2017. U.S. Patent No. 8,701,658 and U.S. Patent No. 9,352,114 will expire on March 17, 2029. U.S. Patent No. 9,592,361 will expire on September 9, 2033. European Patent No. 2265309 will expire on March 17, 2029.

Trademarks

AEROSURF®, AFECTAIR®, SURFAXIN®, SURFAXIN LS™, WINDTREE THERAPEUTICS® (logo), WINDTREE™ and WINDTREE THERAPEUTICS™ are our material registered and common law trademarks.

Trade Secrets

In addition to our patent exclusivities, we rely on trade secrets to protect and maintain our competitive position. We take measures to protect and maintain our trade secrets and know-how licensed to us or developed by us by entering in confidentiality agreements with third parties. Our trade secrets and know-how include information related to manufacturing processes for our drug product candidates and devices, analytical methods and procedures, research and development activities, provisional patent applications, as well as certain information provided to the FDA that was not made public which relates to our regulatory activities and clinical trials.

Other Regulatory Designations

Orphan Drug and Orphan Medicinal Product Designations

The FDA has granted Orphan Drug designation for (i) our KL4 surfactant (lucinactant) for the treatment of RDS in premature infants, (ii) our KL4 surfactant for the prevention and treatment of BPD in premature infants, (iii) our KL4 surfactant for the treatment of ARDS in adults, and (iv) our KL4 surfactant for the treatment of CF. See the section titled "- Government Regulation - Drug Products - Orphan Drugs."

The European Commission, or EC, grants Orphan Medicinal Product designation for pharmaceutical products for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition affecting no more than 5 in 10,000 people which provides for exclusive marketing rights for indications in Europe for 10 years (subject to revision after six years) following marketing approval by the EMA. In addition, the designation would enable us to receive regulatory assistance in the further development process, and to access reduced regulatory fees throughout its marketing life. The EC has granted Orphan Medicinal Product designation for (i) our KL4 surfactant for the prevention of RDS in premature neonates of less than 32 weeks gestational age, (ii) our KL4 surfactant for the treatment of RDS in premature neonates of less than 37 weeks gestational age, (iii) our KL4 surfactant for the treatment of ALI (which in this circumstance encompasses ARDS), and (iv) our KL4 surfactant for the treatment of CF. In submitting the requests to the EMA for Orphan Medicinal Product designations, instead of listing the drug product under the USAN name (lucinactant) as we have in the U.S., we were required to submit our requests under the names of the four APIs in our KL4 surfactant (lucinactant) as follows: sinapultide (KL4), dipalmitoylphosphatidylcholine, palmitoyl-oleoyl phosphatidylglycerol and palmitic acid.

Fast Track Designations

The FDA has granted Fast Track designation for (i) istaroxime for the treatment of AHF, (ii) AEROSURF for the treatment of RDS in premature neonates, and (iii) SURFAXIN® for the prevention and treatment of BPD in premature neonates and the treatment of ARDS in adults. We believe that other of our product candidates may qualify for Fast Track or Breakthrough Therapy designation or other expedited programs. These designations and programs are intended to facilitate and expedite development and review of a New Drug Application, or NDA, to address unmet medical needs in the treatment of serious or life-threatening conditions. See the section titled "- Government Regulation - Drug Products - Fast Track Designation."

Competition

The biotechnology industry is a highly competitive industry. As we work to gain marketing authorization for our product candidates, in some therapeutic areas, competition from numerous existing pharmaceutical companies and other companies entering our fields is expected to be intense and expected to increase. In fact, our future competitors are competing with us currently to secure access to development resources, including clinical sites and their patients to advance development programs. We expect that those companies that are successful at being the first to introduce new products and technologies to the market may gain significant advantages over their competitors in the establishment of a customer base and track record for the performance of their products and technologies. Moreover, there are also existing therapies that may compete with the products we are developing. Therefore, as a development stage biotechnology company, our competitors are comprised of other biotechnology firms and pharmaceutical companies that have existing products or are developing products for our primary markets -- respiratory and cardiovascular indications.

Government Regulation

In the U.S., drug products, medical devices, and drug/medical device combination products are subject to extensive regulation by the FDA. The Federal Food, Drug, and Cosmetic Act, or the FDC Act, and other federal and state statutes and regulations, govern, among other things, the research, development, testing, manufacture, storage, recordkeeping, approval, clearance, labeling, promotion, advertising and marketing, distribution, post-approval monitoring and reporting, sampling, and import and export of drug products, medical devices, and drug/medical device combination products. Failure to comply with applicable U.S. requirements may subject a company to a variety of administrative or judicial sanctions, such as FDA refusal to approve or clear pending new submissions to market drugs or devices warning or untitled letters, product recalls, product seizures, total or partial suspension of production or distribution, injunctions, fines, civil penalties, and criminal prosecution. Drug products, medical devices, and drug/medical device combination products must receive all relevant regulatory approvals or clearances before they may be marketed in the U.S. Drug products, medical devices, and drug/medical device combination products are subject to extensive regulation, including premarket review and marketing authorization, by similar agencies in other countries.

Drug Products

Pharmaceutical product development for a new product or certain changes to an approved product in the U.S. typically involves preclinical laboratory and animal tests, the submission to the FDA of an IND application, which must be accepted before clinical testing may commence, and adequate and well-controlled clinical trials to establish the safety and effectiveness of the drug for each indication for which FDA approval is sought. Satisfaction of FDA pre-market approval requirements typically takes many years and the actual time required may vary substantially based upon the type, complexity, and novelty of the product or disease.

Preclinical tests include laboratory evaluation of product chemistry, formulation, and toxicity, as well as animal trials to assess the characteristics and potential safety and efficacy of the product. The conduct of the preclinical tests must comply with federal regulations and requirements, including good laboratory practices. The results of preclinical testing are submitted to the FDA as part of an IND along with other information, including information about product chemistry, manufacturing and controls, and a proposed clinical trial protocol. Long-term preclinical tests, such as animal tests of reproductive toxicity and carcinogenicity, may continue after the IND is submitted.

A 30-day waiting period after the submission of each IND is required prior to the commencement of clinical testing in humans. If the FDA has neither commented on nor questioned the IND within this 30-day period, the clinical trial proposed in the IND may begin.

Clinical trials involve the administration of the IND to volunteers or patients under the supervision of a qualified investigator. Clinical trials must be conducted: (i) in compliance with federal regulations; (ii) in compliance with GCPs, an international standard meant to protect the rights and health of patients and to define the roles of clinical trial sponsors, administrators, and monitors; as well as (iii) under protocols detailing the objectives of the trial, the parameters to be used in monitoring safety, and the effectiveness criteria to be evaluated. Each protocol involving testing on U.S. patients and subsequent protocol amendments must be submitted to the FDA as part of the IND.

The FDA may order the temporary, or permanent, discontinuation of a clinical trial at any time, or impose other sanctions, if it believes that the clinical trial either is not being conducted in accordance with the FDA requirements or presents an unacceptable risk to the clinical trial patients. The study protocol and informed consent information for patients in clinical trials must also be submitted to an institutional review board, or IRB, for approval. An IRB may also require the clinical trial at the site to be halted, either temporarily or permanently, for failure to comply with the IRB's requirements, or may impose other conditions.

Clinical trials to support NDAs for marketing approval are typically conducted in three sequential phases, but the phases may overlap. In phase 1, the initial introduction of the drug into human subjects or patients, the drug is tested to assess metabolism, pharmacokinetics, pharmacological actions, side effects associated with increasing doses, and, if possible, early evidence on effectiveness. Phase 2 usually involves trials in a limited patient population to determine the effectiveness of the drug for a particular indication, dosage tolerance, and optimum dosage, and to identify common adverse effects and safety risks. If a compound demonstrates evidence of effectiveness and an acceptable safety profile in phase 2 evaluations, phase 3 trials are undertaken to obtain the additional information about clinical efficacy and safety in a larger number of patients, typically at geographically dispersed clinical trial sites, to permit the FDA to evaluate the overall benefit- risk relationship of the drug and to provide adequate information for the labeling of the drug. In most cases the FDA requires two adequate and well-controlled phase 3 clinical trials to demonstrate the efficacy of the drug. A single phase 3 trial with other confirmatory evidence may be sufficient in rare instances where the study is a large multicenter trial demonstrating internal consistency and a statistically very persuasive finding of a clinically meaningful effect on mortality, irreversible morbidity or prevention of a disease with a potentially serious outcome and confirmation of the result in a second trial would be practically or ethically impossible. Data from clinical trials conducted outside the U.S. may be accepted by the FDA subject to certain conditions. For example, the clinical trial must be conducted in accordance with GCPs and the FDA must be able to validate the data from the clinical trial through an onsite inspection if it deems such inspection necessary. Where data from foreign clinical trials are intended to serve as the sole basis for marketing approval in the U.S., the FDA will not approve the application on the basis of foreign data alone unless those data are considered applicable to the U.S. patient population and U.S. medical practice, the clinical trials were performed by clinical investigators of recognized competence, and the data is considered valid without the need for an onsite inspection by the FDA or, if the FDA considers such an inspection to be necessary, the FDA is able to validate the data through an onsite inspection or other appropriate means.

The manufacturer of an investigational drug in a phase 2 or 3 clinical trial for a serious or life-threatening disease is required to make available, such as by posting on its website, its policy on evaluating and responding to requests for expanded access to such investigational drug.

After completion of the required clinical testing, an NDA is prepared and submitted to the FDA. The FDA approval of the NDA is required before marketing of the product may begin in the U.S. The NDA must include the results of all preclinical, clinical, and other testing and a compilation of data relating to the product's pharmacology, chemistry, manufacture, and controls. The cost of preparing and submitting an NDA is substantial. The submission of most NDAs is additionally subject to a substantial application user fee, currently exceeding $2,875,000 for fiscal year 2021, and the applicant under an approved new drug application is also subject to an annual program fee, currently exceeding $336,000 per product for fiscal year 2021. These fees are typically increased annually.

The FDA has 60 days from its receipt of an NDA to determine whether the application will be filed based on the agency's threshold determination that it is sufficiently complete to permit substantive review. If the NDA submission is filed, the FDA reviews the NDA to determine, among other things, whether the proposed product is safe and effective for its intended use. The FDA has agreed to certain performance goals in the review of NDAs. Most such applications for standard review drug products are reviewed within ten to twelve months; most applications for priority review drugs are reviewed in six to eight months. Priority review can be applied to drugs that the FDA determines offer major advances in treatment or provide a treatment where no adequate therapy exists. The review process for both standard and priority review may be extended by the FDA for three additional months to consider certain late-submitted information, or information intended to clarify information already provided in the submission.

The FDA may also refer applications for novel drug products, or drug products that present difficult questions of safety or efficacy, to an advisory committee - typically a panel that includes clinicians and other experts - for review, evaluation, and a recommendation as to whether the application should be approved. The FDA is not bound by the recommendation of an advisory committee, but it generally follows such recommendations. Before approving an NDA, the FDA will typically inspect one or more clinical sites to assure compliance with GCPs. Additionally, the FDA will inspect the facility or the facilities at which the drug is manufactured. The FDA will not approve the product unless compliance with current good manufacturing practices, or cGMPs, is satisfactory and the NDA contains data that provide substantial evidence that the drug is safe and effective in the indication studied.

After the FDA evaluates the NDA and the manufacturing facilities, it issues either an approval letter or a complete response letter. A complete response letter generally outlines the deficiencies in the submission and may require substantial additional testing, or information, in order for the FDA to reconsider the application. If, or when, those deficiencies have been addressed to the FDA's satisfaction in a resubmission of the NDA, the FDA will issue an approval letter. The FDA has committed to reviewing such resubmissions in two or six months depending on the type of information included.

An approval letter authorizes commercial marketing of the drug with specific prescribing information for specific indications. As a condition of NDA approval, the FDA may require a Risk Evaluation and Mitigation Strategy, or REMS, to help ensure that the benefits of the drug outweigh the potential risks. REMS can include medication guides, communication plans for healthcare professionals, and elements to assure safe use, or ETASU. ETASU can include, but are not limited to, special training or certification for prescribing or dispensing, dispensing only under certain circumstances, special monitoring, and the use of patient registries. The requirement for a REMS can materially affect the potential market and profitability of the drug. Moreover, product approval may require substantial post-approval testing and surveillance to monitor the drug's safety or efficacy. Once granted, product approvals may be withdrawn if compliance with regulatory standards is not maintained or problems are identified following initial marketing.

Changes to some of the conditions established in an approved application, including changes in indications, labeling, or manufacturing processes or facilities, require submission and the FDA approval of a new NDA or NDA supplement before the change can be implemented. An NDA supplement for a new indication typically requires clinical data similar to that in the original application, and the FDA uses the same procedures and actions in reviewing NDA supplements as it does in reviewing NDAs.

Orphan Drugs

Under the Orphan Drug Act, the FDA may grant Orphan Drug designation to drugs intended to treat a rare disease or condition - generally a disease or condition that affects fewer than 200,000 individuals in the U.S. Orphan drug designation must be requested before submitting an NDA. After the FDA grants Orphan Drug designation, the generic identity of the drug and its potential orphan use are disclosed publicly by the FDA. Orphan drug designation does not convey any advantage in, or shorten the duration of, the regulatory review and approval process. The first NDA applicant to receive FDA approval for a particular active moiety to treat a particular disease with FDA Orphan Drug designation is entitled to a seven- year exclusive marketing period in the U.S. for that product, for that indication. During the seven-year exclusivity period, the FDA may not approve any other applications to market the same drug for the same disease, except in limited circumstances, such as a showing of clinical superiority to the product with Orphan Drug exclusivity by means of greater effectiveness, greater safety, or providing a major contribution to patient care. Orphan drug exclusivity does not prevent the FDA from approving a different drug for the same disease or condition, or the same drug for a different disease or condition. Among the other benefits of Orphan Drug designation are tax credits for certain research and a waiver of the NDA application user fee.

Fast Track Designation

The FDA is required to facilitate the development, and expedite the review, of drugs that are intended for the treatment of a serious or life-threatening disease and which demonstrate the potential to address unmet medical needs for the condition. Under the Fast Track program, the sponsor of a new drug candidate may request that the FDA designate the drug candidate for a specific indication as a Fast Track drug concurrent with, or after, the filing of the IND for the drug candidate. The FDA must determine if the drug candidate qualifies for Fast Track designation within 60 days of receipt of the sponsor's request.

Under the Fast Track program, sponsors have the opportunity to engage in more frequent interactions with the FDA. In addition, the FDA may initiate review of sections of a Fast Track drug's NDA before the application is complete. This rolling review is available if the applicant provides, and the FDA approves, a schedule for the submission of the remaining information and the applicant pays applicable user fees. However, the FDA's time period goal for reviewing an application does not begin until the last section of the NDA is submitted. Additionally, the Fast Track designation may be withdrawn by the FDA if the FDA believes that the designation is no longer supported by data emerging in the clinical trial process.

Breakthrough Therapy Designation

FDA is also required to expedite the development and review of the application for approval of drugs that are intended to treat a serious or life-threatening disease or condition where preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints. Under the Breakthrough Therapy program, the sponsor of a new drug candidate may request that FDA designate the drug candidate for a specific indication as a Breakthrough Therapy concurrent with, or after, the filing of the IND for the drug candidate. FDA must determine if the drug candidate qualifies for Breakthrough Therapy designation within 60 days of receipt of the sponsor's request.

The Hatch-Waxman Act

Orange Book Listing

In seeking approval for a drug through an NDA, applicants are required to list with the FDA each patent with claims covering the applicant's product or method of using the product. Upon approval of a drug, each of the patents listed in the application for the drug is then published in the FDA's Approved Drug Products with Therapeutic Equivalence Evaluations, commonly known as the Orange Book. Drugs listed in the Orange Book can, in turn, be cited by potential generic competitors in support of approval of an abbreviated new drug application, or ANDA. An ANDA provides for marketing of a drug product that has the same active ingredients in the same strengths and dosage form as the listed drug and has been shown to be bioequivalent to the listed drug. Other than the requirement for bioequivalence testing, ANDA applicants are not required to conduct, or submit results of, preclinical or clinical tests to prove the safety or effectiveness of their drug product. Drugs approved in this way are commonly referred to as generic equivalents to the listed drug, and can often be substituted by pharmacists under prescriptions written for the original listed drug.

The ANDA applicant is required to certify to the FDA concerning any patents listed for the approved product in the FDA's Orange Book. Specifically, the applicant must certify that: (i) the required patent information has not been filed; (ii) the listed patent has expired; (iii) the listed patent has not expired, but will expire on a particular date and approval is sought after patent expiration; or (iv) the listed patent is invalid or will not be infringed by the new product. The ANDA applicant may also elect to submit a Section VIII statement certifying that its proposed ANDA labeling does not contain (or carves out) any language regarding the patented method-of-use rather than certify to a listed method-of-use patent. If the applicant does not challenge the listed patents, the ANDA application will not be approved until all the listed patents claiming the referenced product have expired.

A certification that the new product will not infringe the already approved product's listed patents, or that such patents are invalid, is called a Paragraph IV certification. If the ANDA applicant has provided a Paragraph IV certification to the FDA, the applicant must also send notice of the Paragraph IV certification to the NDA and patent holders once the ANDA has been received by the FDA. The NDA and patent holders may then initiate a patent infringement lawsuit in response to the notice of the Paragraph IV certification. The filing of a patent infringement lawsuit within 45 days of the receipt of a Paragraph IV certification automatically prevents the FDA from approving the ANDA until the earlier of 30 months, expiration of the patent, settlement of the lawsuit, or a decision in the infringement case that is favorable to the ANDA applicant.

An applicant submitting an NDA under Section 505(b)(2) of the FDC Act, which permits the filing of an NDA where at least some of the information required for approval comes from studies not conducted by, or for, the applicant and for which the applicant has not obtained a right of reference, is required to certify to the FDA regarding any patents listed in the Orange Book for the approved product it references to the same extent that an ANDA applicant would.

Market Exclusivity

Market exclusivity provisions under the FDC Act also can delay the submission or the approval of certain applications. The FDC Act provides a five-year period of non-patent exclusivity within the U.S. to the first applicant to gain approval of an NDA for a new chemical entity, or NCE. A drug is entitled to NCE exclusivity if it contains a drug substance no active moiety of which has been previously approved by the FDA. During the exclusivity period, the FDA may not receive for review an ANDA or file a 505(b)(2) NDA submitted by another company for another version of such drug where the applicant does not own or have a legal right of reference to all the data required for approval. However, an application may be submitted after four years if it contains a Paragraph IV certification. The FDC Act also provides three years of market exclusivity for an NDA, 505(b)(2) NDA or supplement to an existing NDA if new clinical investigations, other than bioavailability studies, that were conducted or sponsored by the applicant are deemed by the FDA to be essential to the approval of the application, for example, for new indications, dosages or strengths of an existing drug. This three-year exclusivity covers only the conditions for use associated with the new clinical investigations and does not prohibit the FDA from approving ANDAs for drugs for the original conditions of use, such as the originally approved indication. Five-year and three-year exclusivity will not delay the submission or approval of a full NDA; however, an applicant submitting a full NDA would be required to conduct or obtain a right of reference to all the non-clinical studies and adequate and well- controlled clinical trials necessary to demonstrate safety and effectiveness.

Patent Term Extension

After NDA approval, the owner of a relevant drug patent may apply for up to five years of patent term extension. Only one patent may be extended for each regulatory review period, which is composed of two parts: a testing phase, and an approval phase. The allowable patent term extension is calculated as half of the drug's testing phase - the time between the day the IND becomes effective and NDA submission - and all of the review phase - the time between NDA submission and approval - up to a maximum of five years. The time can be shortened if the FDA determines that the applicant did not pursue approval with due diligence. The total remaining patent term after the extension may not exceed 14 years.

For patents that might expire during the application phase, the patent owner may request an interim patent extension. An interim patent term extension increases the patent term by one year and may be renewed up to four times. For each interim patent term extension granted, the post-approval patent term extension is reduced by one year. The director of the United States Patent and Trademark Office, or USPTO, must determine that approval of the drug covered by the patent for which a patent extension is being sought is likely. Interim patent term extensions are not available for a drug for which an NDA has not been submitted.

Post-Approval Requirements

Once an NDA is approved, a product will be subject to certain post-approval requirements. For instance, the FDA closely regulates the post-approval marketing and promotion of drugs, including standards and regulations for direct-to- consumer advertising, off-label promotion, industry-sponsored scientific and educational activities and promotional activities involving the internet. Drugs may be marketed only for the approved indications and in accordance with the provisions of the approved labeling.

Adverse event reporting and submission of periodic reports is required following FDA approval of an NDA. The FDA also may require post-marketing testing, known as phase 4 testing, REMS, and surveillance to monitor the effects of an approved product, or the FDA may place conditions on an approval that could restrict the distribution or use of the product. In addition, quality-control, drug manufacture, packaging, and labeling procedures must continue to conform to cGMPs, after approval. Drug manufacturers and certain of their subcontractors are required to register their establishments with the FDA and certain state agencies. Registration with the FDA subjects entities to periodic unannounced inspections by the FDA, during which the agency inspects manufacturing facilities to assess compliance with cGMPs. Accordingly, manufacturers must continue to expend time, money, and effort in the areas of production and quality-control to maintain compliance with cGMPs. Regulatory authorities may withdraw product approvals or request product recalls if a company fails to comply with regulatory standards, if it encounters problems following initial marketing, or if previously unrecognized problems are subsequently discovered. In addition, prescription drug manufacturers in the U.S. must comply with applicable provisions of the Drug Supply Chain Security Act and provide and receive product tracing information, maintain appropriate licenses, ensure they only work with other properly licensed entities, and have procedures in place to identify and properly handle suspect and illegitimate products.

Pediatric Information

Under the Pediatric Research Equity Act, or PREA, NDAs or supplements to NDAs must contain data to assess the safety and effectiveness of the drug for the claimed indications in all relevant pediatric subpopulations and to support dosing and administration for each pediatric subpopulation for which the drug is safe and effective. The FDA may grant full or partial waivers, or deferrals, for submission of data. Unless otherwise required by regulation, PREA does not apply to any drug for an indication for which orphan designation has been granted except a product with a new active ingredient that is a molecularly targeted cancer product intended for the treatment of an adult cancer and directed at a molecular target determined by the FDA to be substantially relevant to the growth or progression of a pediatric cancer that is subject to an NDA or Biologics License Application, or BLA, submitted on or after August 18, 2020.

The Best Pharmaceuticals for Children Act, or BPCA, provides NDA holders a six-month extension of any exclusivity—patent or non-patent—for a drug if certain conditions are met. Conditions for exclusivity include the FDA's determination that information relating to the use of a new drug in the pediatric population may produce health benefits in that population, the FDA making a written request for pediatric studies, and the applicant agreeing to

perform, and reporting on, the requested studies within the statutory timeframe. Applications under the BPCA are treated as priority applications, with all of the benefits that designation confers.

Disclosure of Clinical Trial Information

Sponsors of clinical trials of FDA-regulated products are required to register and disclose certain clinical trial information. Information related to the product, patient population, phase of investigation, trial sites and investigators, and other aspects of the clinical trial is then made public as part of the registration. Sponsors are also obligated to discuss the results of their clinical trials after completion. Disclosure of the results of these trials can be delayed in certain circumstances for up to two years after the date of completion of the trial. Competitors may use this publicly available information to gain knowledge regarding the progress of development programs.

Medical Device Products

A medical device is an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component part, or accessory which is: (i) recognized in the official National Formulary, or the US Pharmacopoeia, or any supplement to them; (ii) intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals; or (iii) intended to affect the structure or any function of the body of man or other animals, and which does not achieve any of its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of any of its primary intended purposes.

The FDC Act classifies medical devices into one of three categories based on the risks associated with the device and the level of control necessary to provide reasonable assurance of safety and effectiveness. Class I devices are deemed to be low risk and are subject to the fewest regulatory controls. Class III devices are generally the highest risk devices and are subject to the highest level of regulatory control to provide reasonable assurance of the device's safety and effectiveness. Class III devices must typically be approved by the FDA before they are marketed.

Generally, establishments that manufacture and/or distribute devices, including manufacturers, contract manufacturers, sterilizers, repackagers and relabelers, specification developers, reprocessors of single-use devices, remanufacturers, initial importers, manufacturers of accessories and components sold directly to the end user, and U.S. manufacturers of export-only devices, are required to register their establishments with the FDA and provide the FDA a list of the devices that they handle at their facilities.

Pre-market Authorization and Notification

While most Class I and some Class II devices can be marketed without prior FDA authorization, most medical devices can be legally sold within the U.S. only if the FDA has: (i) approved a premarket approval application, or PMA, prior to marketing, generally applicable to Class III devices; or (ii) cleared the device in response to a premarket notification, or 510(k) submission, generally applicable to Class I and II devices. Some devices that have been classified as Class III are regulated pursuant to the 510(k) requirements because the FDA has not yet called for PMAs for these devices. Other less common regulatory pathways to market for certain devices include the de novo classification process, the humanitarian device exception, or a product development protocol.

The 510(k) Clearance Process

Under the 510(k) process, the manufacturer must submit to the FDA a premarket notification, demonstrating that the device is "substantially equivalent," as defined in the statute, to a legally marketed predicate device.

A predicate device is a legally marketed device that is not subject to premarket approval, i.e., a device that was legally marketed prior to May 28, 1976, often referred to as a preamendments device, and for which a PMA is not required, a device that has been reclassified from Class III to Class II or I, or a device that was previously found substantially equivalent through the 510(k) process. To be "substantially equivalent," the proposed device must have the same intended use as the predicate device, and either have the same technological characteristics as the predicate device or have different technological characteristics and not raise different questions of safety or effectiveness than the predicate device. Clinical data is sometimes required to support substantial equivalence.

After a 510(k) premarket notification is submitted, the FDA determines whether to accept it for substantive review. If it lacks necessary information for substantive review, the FDA will refuse to accept the 510(k) notification. If it is accepted for filing, the FDA begins a substantive review. By statute, the FDA has a performance goal to complete its review of 95% of 510(k) submissions within 90 days of receipt. As a practical matter, clearance often takes longer, because the FDA can request additional date and information, which pauses the review clock for up to 180 days, and clearance is never assured. Although many 510(k) premarket notifications are cleared without clinical data, the FDA may require further information, including clinical data, to make a determination regarding substantial equivalence. If the FDA agrees that the device is substantially equivalent, it will grant clearance to commercially market the device.

If the FDA determines that the device is not "substantially equivalent" to a predicate device, or if the device is automatically classified into Class III, the device sponsor must then fulfill the much more rigorous premarketing requirements of the PMA approval process, or seek reclassification of the device through the de novo process. A manufacturer can also submit a petition for direct de novo review if the manufacturer is unable to identify an appropriate predicate device and the new device or new use of the device presents a moderate or low risk.

After a device receives 510(k) clearance, any modification that could significantly affect its safety or effectiveness, or that would constitute a new or major change in its intended use, will require a new 510(k) clearance or, depending on the modification, could require a PMA application or de novo classification. The FDA requires each manufacturer to determine whether the proposed change requires submission of a 510(k) or a PMA in the first instance, but the FDA can review any such decision and disagree with a manufacturer's determination. Many minor modifications are accomplished by a letter-to- file in which the manufacturer documents the change in an internal letter-to-file. The letter-to-file is in lieu of submitting a new 510(k) to obtain clearance for such change. The FDA can always review these letters to file in an inspection. If the FDA disagrees with a manufacturer's determination regarding whether a new premarket submission is required for the modification of an existing device, the FDA can require the manufacturer to cease marketing and/or recall the modified device until 510(k) clearance or approval of a PMA application is obtained. In addition, in these circumstances, the FDA can impose significant regulatory fines or penalties for failure to submit the requisite PMA application(s).

The PMA Approval Process

Following receipt of a PMA application, the FDA conducts an administrative review to determine whether the application is sufficiently complete to permit a substantive review. If it is not, the agency will refuse to file the PMA. If it is, the FDA will accept the application for filing and begin the review. The FDA, by statute and by regulation, has a performance goal to review 90% of PMA applications within 180 days, if advisory committee input is not required, and within 320 days, if advisory committee input is required, although the review of an application more often occurs over a significantly longer period of time. During this review period, the FDA may request additional information or clarification of information already provided, and the FDA may issue a major deficiency letter to the applicant, requesting the applicant's response to deficiencies communicated by the FDA. The FDA considers a PMA or PMA supplement to have been voluntarily withdrawn if an applicant fails to respond to an FDA request for information (i.e., major deficiency letter) within a total of 360 days. Before approving or denying a PMA, an FDA advisory committee may review the PMA at a public meeting and provide the FDA with the committee's recommendation on whether the FDA should approve the submission, approve it with specific conditions, or not approve it. The FDA is not bound by the recommendations of an advisory committee, but it considers such recommendations carefully when making decisions.

Prior to approval of a PMA, the FDA may conduct inspections of the clinical trial data and clinical trial sites, as well as inspections of the manufacturing facility and processes. Overall, the FDA review of a PMA application generally takes between one and three years, but may take significantly longer. The FDA can delay, limit or deny approval of a PMA application for many reasons, including:

- the device may not be shown safe or effective to the FDA's satisfaction;
- the data from preclinical studies and/or clinical trials may be found unreliable or insufficient to support approval;
- the manufacturing process or facilities may not meet applicable requirements; and
- changes in FDA approval policies or adoption of new regulations may require additional data.

If the FDA evaluation of a PMA is favorable, the FDA will issue either an approval letter, or an approvable letter, the latter of which usually contains a number of conditions that must be met in order to secure final approval of the PMA. When and if those conditions have been fulfilled to the satisfaction of the FDA, the agency will issue a PMA approval letter authorizing commercial marketing of the device, subject to the conditions of approval and the limitations established in the approval letter. If the FDA's evaluation of a PMA application or manufacturing facilities is not favorable, the FDA will deny approval of the PMA or issue a not approvable letter. The FDA also may determine that additional tests or clinical trials are necessary, in which case the PMA approval may be delayed for several months or years while the trials are conducted and data is submitted in an amendment to the PMA, or the PMA is withdrawn and resubmitted when the data are available. The PMA process can be expensive, uncertain and lengthy and a number of devices for which the FDA approval has been sought by other companies have never been approved by the FDA for marketing.

New PMA applications or PMA supplements are required for modification to the manufacturing process, equipment or facility, quality control procedures, sterilization, packaging, expiration date, labeling, device specifications, ingredients, materials or design of a device that has been approved through the PMA process. PMA supplements often require submission of the same type of information as an initial PMA application, except that the supplement is limited to information needed to support any changes from the device covered by the approved PMA application and may or may not require as extensive technical or clinical data or the convening of an advisory panel, depending on the nature of the proposed change. In approving a PMA application, as a condition of approval, the FDA may also require some form of post-approval study or post-market surveillance, whereby the applicant conducts a follow-up study or follows certain patient groups for a number of years and makes periodic reports to the FDA on the clinical status of those patients when necessary to protect the public health or to provide additional or longer term safety and effectiveness data for the device. The FDA may also require post-market surveillance for certain devices cleared under a 510(k) notification, such as implants or life-supporting or life- sustaining devices used outside a device user facility. The FDA may also approve a PMA application with other post-approval conditions intended to ensure the safety and effectiveness of the device, such as, among other things, restrictions on labeling, promotion, sale, distribution and use.

Exempt Devices

If a manufacturer's device falls into a generic category of Class I or Class II devices that the FDA has exempted by regulation, a premarket notification is not required before marketing the device in the U.S. Manufacturers of such devices are required to register their establishments and list the proprietary device name and the generic category or classification regulation into which the device fits. Some 510(k)-exempt devices are also exempt from Quality System Regulation, or QSR, requirements.

Post-market Requirements

After a device is placed on the market, numerous regulatory requirements apply. These include: the QSR, labeling regulations, the FDA's general prohibition against promoting products for unapproved or off-label uses, the Medical Device Reporting regulation (which requires that manufacturers report to the FDA if their device may have caused or contributed to a death or serious injury or malfunctioned in a way that would likely cause or contribute to a death or serious injury if it were to recur), and the Reports of Corrections and Removals regulation (which requires manufacturers to report recalls and field actions to the FDA if initiated to reduce a risk to health posed by the device or to remedy a violation of the FDC Act).

The FDA enforces these requirements by inspection and market surveillance. If the FDA finds a violation, it can institute a wide variety of enforcement actions, ranging from a public warning letter to more severe sanctions such as: fines, injunctions, and civil penalties; recall or seizure of products; operating restrictions, partial suspension or total shutdown of production; refusing requests for 510(k) clearance or PMA approval of new products; withdrawing 510(k) clearance or PMA approvals already granted; and criminal prosecution.

Combination Products

A combination product is a product comprised of (i) two or more regulated components, i.e., drug/medical device, biologic/medical device, drug/biologic, or drug/medical device/biologic, that are physically, chemically, or otherwise combined or mixed and produced as a single entity; (ii) two or more separate products packaged together in a single package or as a unit and comprised of drug and device products, device and biological products, or biological and drug products; (iii) a drug, device, or biological product packaged separately that according to its investigational plan or proposed labeling is intended for use only with an approved individually specified drug, device, or biological product where both are required to achieve the intended use, indication, or effect and where, upon approval of the proposed product, the labeling of the approved product would need to be changed, i.e., to reflect a change in intended use, dosage form, strength, route of administration, or significant change in dose; or (iv) any investigational drug, device, or biological product packaged separately that according to its proposed labeling is for use only with another individually specified investigational drug, device, or biological product where both are required to achieve the intended use, indication, or effect.

The FDA is divided into various branches, or Centers, by product type. Different Centers typically review drug, biologic, or device applications. In order to review an application for a combination product, the FDA must decide which Center should be responsible for the review. FDA regulations require that the FDA determine the combination product's primary mode of action, or PMOA, which is the single mode of a combination product that provides the most important therapeutic action of the combination product. The Center that regulates that portion of the product that generates the PMOA becomes the lead evaluator. If there are two independent modes of action, neither of which is subordinate to the other, the FDA makes a determination as to which Center to assign the product based on consistency with other combination products raising similar types of safety and effectiveness questions or to the Center with the most expertise in evaluating the most significant safety and effectiveness questions raised by the combination product. When evaluating an application, a lead Center may consult other Centers but still retain complete reviewing authority, or it may collaborate with another Center, by which the Center assigns review of a specific section of the application to another Center, delegating its review authority for that section. Typically, the FDA requires a single marketing application submitted to the Center selected to be the lead evaluator, although the agency has the discretion to require separate applications to more than one Center. One reason to submit multiple evaluations is if the applicant wishes to receive some benefit that accrues only from approval under a particular type of application, like new drug product exclusivity. If multiple applications are submitted, each may be evaluated by a different lead Center.

Regulation Outside the U.S.

In addition to regulations in the U.S., we are subject to a variety of regulations in other jurisdictions governing clinical studies, commercial sales, and distribution of our products. Most countries outside the U.S. require that clinical trial applications be submitted to and approved by the local regulatory authority for each clinical study. In addition, whether or not we obtain FDA approval for a product, we must obtain approval of a product by the comparable regulatory authorities of countries outside the U.S. before we can commence clinical studies or marketing of the product in those countries. The approval process varies from country to country, and the time may be longer or shorter than that required for FDA approval.

To obtain regulatory approval of an Orphan Drug under EU regulatory systems, we are mandated to submit marketing authorization applications, or MAAs, in centralized procedure. The centralized procedure, which came into operation in 1995, allows applicants to obtain a marketing authorization that is valid throughout the EU. It is compulsory for medicinal products manufactured using biotechnological processes, for orphan medicinal products and for human products containing a new active substance which was not authorized in the Community before May 20, 2004 (date of entry into force of Regulation (EC) No 726/2004) and which are intended for the treatment of AIDS, cancer, neurodegenerative disorder or diabetes. The centralized procedure is optional for any other products containing new active substances not authorized in the Community before May 20, 2004 or for products which constitute a significant therapeutic, scientific or technical innovation or for which a Community authorization is in the interests of patients at Community level. When a company wishes to place on the market a medicinal product that is eligible for the centralized procedure, it sends an application directly to the EMA, to be assessed by the Committee for Medicinal Products for Human Use, or CHMP. The procedure results in an EC decision, which is valid in all EU Member States. Centrally-authorized products may be marketed in all EU Member States.

In centralized procedure, full copies of the MAA are sent to a rapporteur and a co-rapporteur designated by the competent EMA scientific committee. They coordinate the EMA's assessment of the medicinal product and prepare draft reports. Once the draft reports are prepared (other experts might be called upon for this purpose), they are sent to the CHMP, whose comments or objections are communicated to the applicant. The rapporteur is therefore the privileged interlocutor of the applicant and continues to play this role, even after the MAA has been granted. The rapporteur and co-rapporteur then assess the applicant's replies, submit them for discussion to the CHMP and, taking into account the conclusions of this debate, prepare a final assessment report. Once the evaluation is completed, the CHMP gives a favorable or unfavorable opinion as to whether to grant the authorization. When the opinion is favorable, it shall include the draft summary of the product's characteristics, the package leaflet and the texts proposed for the various packaging materials. The time limit for the evaluation procedure is 210 days. The EMA then has fifteen days to forward its opinion to the EC. This is the start of the second phase of the procedure: the decision-making process.

The EMA sends to the EC its opinion and assessment report, together with annexes containing: the SmPC (Annex 1); the particulars of the Marketing Authorisation Holder, or MAH, responsible for batch release, the particulars of the manufacturer of the active substance and the conditions of the marketing authorization (Annex 2); and the labeling and the package leaflet (Annex 3). The annexes are translated into the 22 other official languages of the EU. During the decision-making process, the EC services verify that the marketing authorization complies with EU law. The EC has fifteen days to prepare a draft decision. The medicinal product is assigned a Community registration number, which will be placed on its packaging if the marketing authorization is granted. During this period, various EC directorates general are consulted on the draft marketing authorization decision. The draft decision is then sent to the Standing Committee on Medicinal Products for Human Use (EU Member States have one representative each in both of these committees) for their opinions.

The centralized procedure, which is compulsory for medicines produced by certain biotechnological processes and optional for those which are highly innovative, provides for the grant of a single marketing authorization that is valid for all EU member states. The decentralized procedure provides for approval by one or more other, or concerned, member states of an assessment of an application performed by one member state, known as the reference member state. Under this procedure, an applicant submits an application, or dossier, and related materials including a draft summary of product characteristics, and draft labeling and package leaflet, to the reference member state and concerned member states. The reference member state prepares a draft assessment and drafts of the related materials within 120 days after receipt of a valid application. Within 90 days of receiving the reference member state's assessment report, each concerned member state must decide whether to approve the assessment report and related materials. If a member state cannot approve the assessment report and related materials on the grounds of potential serious risk to the public health, the disputed points may eventually be referred to the EC, whose decision is binding on all member states.

Applications from persons or companies seeking "orphan medicinal product designation" for products they intend to develop for the diagnosis, prevention, or treatment of life-threatening or very serious conditions that affect not more than 5 in 10,000 persons in the EU are reviewed by the Committee for Orphan Medicinal Products, or COMP. In addition, Orphan Drug designation can be granted if the drug is intended for a life threatening, seriously debilitating, or serious and chronic condition in the EU and that without incentives it is unlikely that sales of the drug in the EU would be sufficient to justify developing the drug. Orphan drug designation is only available if there is no other satisfactory method approved in the EU of diagnosing, preventing, or treating the condition, or if such a method exists, the proposed Orphan Drug will be of significant benefit to patients. Orphan drug designation provides opportunities for fee reductions for protocol assistance and access to the centralized regulatory procedures before and during the first year after marketing approval, which reductions are not limited to the first year after marketing approval for small and medium enterprises. In addition, if a product which has an Orphan Drug designation subsequently receives EMA marketing approval for the indication for which it has such designation, the product is entitled to Orphan Drug exclusivity, which means the EMA may not approve any other application to market the same drug for the same indication for a period of 10 years. The exclusivity period may be reduced to six years if the designation criteria are no longer met, including where it is shown that the product is sufficiently profitable not to justify maintenance of market exclusivity. Competitors may receive marketing approval of different drugs or biologics for the indications for which the orphan product has exclusivity. In order to do so, however, they must demonstrate that the new drugs or biologics provide a significant benefit over the existing orphan product. This demonstration of significant benefit may be done at the time of initial approval or in post-approval studies, depending on the type of marketing authorization granted.

A pediatric investigation plan, or PIP, is a development plan aimed at ensuring that the necessary data are obtained to support the authorization of a medicine for children, through studies in children. All applications for marketing authorization for new medicines have to include the results of studies as described in an agreed PIP, unless the medicine is exempt because of a deferral or waiver. This requirement also applies when a marketing-authorization holder wants to add a new indication, pharmaceutical form, or route of administration for a medicine that is already authorized and covered by intellectual property rights. Several rewards and incentives for the development of pediatric medicines for children are available in the EU. Medicines authorized across the EU with the results of studies from a PIP included in the product information are eligible for an extension of their supplementary protection certificate by six months. This is the case even when the studies' results are negative. For orphan medicines, the incentive is an additional two years of market exclusivity. Scientific advice and protocol assistance at the EMA are free of charge for questions relating to the development of pediatric medicines. Medicines developed specifically for children that are already authorized but are not protected by a patent or supplementary protection certificate are eligible for a pediatric-use marketing authorization, or PUMA. If a PUMA is granted, the product will benefit from 10 years of market protection as an incentive.

The European Union Medical Devices Directive, or MDD, sets out the basic regulatory framework for medical devices in the EU. This directive has been separately enacted in more detail in the national legislation of the individual member states of the EU. On April 5, 2017, the European Parliament passed the Medical Devices Regulation (Regulation 2017/745), or MDR, which repeals and replaces the MDD and the Active Implantable Medical Devices Directive. The changes were prompted by divergent interpretations of the current directives and to address issues concerning product quality and performance. The MDR went into effect on May 26, 2021, and it:

- strengthens the rules on placing devices on the market and reinforces surveillance once they are available;
- establishes explicit provisions on manufacturers' responsibilities for the follow-up of the quality, performance, and safety of devices placed on the market;
- improves the traceability of medical devices throughout the supply chain to the end-user or patient through a unique identification number;
- sets up a central database to provide patients, healthcare professionals, and the public with comprehensive information on products available in the EU; and
- strengthens rules for the assessment of certain high-risk devices, such as implants, which may have to undergo an additional check by experts before they are placed on the market.

Under both the MDD and the MDR, the system of regulating medical devices operates by way of a certification for each medical device. Each certificated device is marked with a Conformitè Europëenne mark, or CE mark, which shows that the device has a Certificat de Conformité, also referred to as a Certificate of Conformance. There are national bodies known as Competent Authorities in each member state which oversee the implementation of the MDD (and now the MDR) within their jurisdiction. The means for achieving the requirements for CE mark varies according to the nature of the device. Devices are classified in accordance with their perceived risks, similarly to the U.S. system. The class of a product determines the requirements to be fulfilled before a CE mark can be placed on a product, known as a conformity assessment. Conformity assessments for products are carried out as required by the MDD (and now the MDR). Except for low-risk medical devices (Class I non-sterile, non-measuring devices), where the manufacturer can self-certify compliance with the MDD (and now the MDR) based on a self-assessment of the conformity of its products with the essential requirements of the EU MDD, a conformity assessment procedure requires the intervention of an organization accredited by a member state of the European Economic Area, or EEA, to conduct conformity assessments, or a Notified Body. If a Notified Body of one member state has issued a Certificat de Conformité, the device can be sold throughout the EU without further conformance tests being required in other member states.

Under transitional provisions provided in the MDR, medical devices that had valid CE Certificates of Conformity issued under the MDD prior to May 26, 2021 may, provided related obligations are respected, continue to be placed on the EEA market for the remaining validity of the certificate, and until May 27, 2024 at the latest. After the expiry of any applicable transitional period, only devices that have been CE marked on the basis of the MDR may be placed on the market in the EEA.

Post-Brexit, the MDR does not apply in the United Kingdom, or UK, (except for Northern Ireland, which under the Northern Irish Protocol is bound by certain EU laws). The medical device legislative framework in the UK is set out in the Medical Devices Regulations 2002. These regulations are based on the previous medical device directives of the EU, but have been amended so that they function properly now that the UK is no longer part of the EU. The Medical Devices Regulations 2002 have introduced several changes including (but not limited to) replacing the CE mark with a UK Conformity Assessed marking (although EU CE marks will be recognized until June 30, 2023), requiring manufacturers outside of the UK to appoint a UK Responsible Person if they place devices on the market in the UK and more wide-ranging device registration requirements.

In addition, there are new regulations for in vitro diagnostics, Regulation (EU) 2017/746 on In-Vitro Diagnostic Devices, and these will fully apply beginning in May 2022.

International Approvals

Drug products, medical devices, and drug/medical device combination products are subject to extensive regulation, including premarket review and marketing authorization, by similar agencies in other countries. Regulatory requirements and approval processes are similar in approach to that of the U.S. but are not harmonized. International regulators are independent and not bound by the findings of the FDA and there is a risk that foreign regulators will not accept clinical trial design/results or may require additional data or other information not requested by the FDA. In addition, international regulators may require different manufacturing practices than the FDA's cGMPs.

Reimbursement

Potential sales of any of our product candidates, if approved, will depend, at least in part, on the extent to which such products will be covered by third-party payors, such as government health care programs, commercial insurance and managed healthcare organizations. These third-party payors are increasingly limiting coverage and/or reducing reimbursements for medical products and services. A third-party payor's decision to provide coverage for a drug product does not imply that an adequate reimbursement rate will be approved. Further, one payor's determination to provide coverage for a drug product does not assure that other payors will also provide coverage for the drug product. In addition, the U.S. government, state legislatures and foreign governments have continued implementing cost-containment programs, including price controls, restrictions on reimbursement and requirements for substitution of generic products. Adoption of price controls and cost-containment measures, and adoption of more restrictive policies in jurisdictions with existing controls and measures, could further limit our future revenues and results of operations. Decreases in third-party reimbursement or a decision by a third-party payor to not cover a product candidate, if approved, or any future approved products could reduce physician usage of our products, and have a material adverse effect on our sales, results of operations and financial condition.

In the U.S., the Medicare Part D program provides a voluntary outpatient drug benefit to Medicare beneficiaries for certain products. We do not know whether our product candidates, if approved, will be eligible for coverage under Medicare Part D, but individual Medicare Part D plans offer coverage subject to various factors such as those described above. Furthermore, private payors often follow Medicare coverage policies and payment limitations in setting their own coverage policies.

Anti-Kickback, False Claims Laws and Other Regulations

In addition to the FDA restrictions on marketing of pharmaceutical products, medical devices, and combination products, several other types of state and federal laws have been applied to restrict certain marketing practices in the medical product industry in recent years. These laws include anti-kickback statutes, false claims statutes, and other statutes pertaining to health care fraud and abuse. The federal healthcare program anti-kickback statute prohibits, among other things, knowingly and willfully offering, paying, soliciting or receiving remuneration to induce, or in return for, purchasing, leasing, ordering or arranging for the purchase, lease or order of any healthcare item or service reimbursable under Medicare, Medicaid, or other federally financed healthcare programs. The Patient Protection and Affordable Care Act, or PPACA, amended the intent element of the federal statute so that a person or entity no longer needs to have actual knowledge of the statute or specific intent to violate it. This statute has been interpreted to apply to arrangements between pharmaceutical manufacturers on the one hand and prescribers, purchasers, and formulary managers on the other. Violations of the anti-kickback statute are punishable by imprisonment, criminal fines, civil monetary penalties, and exclusion from participation in federal healthcare programs. Although there are a number of statutory exemptions and regulatory safe harbors protecting certain common activities from prosecution or other regulatory sanctions, the exemptions and safe harbors are drawn narrowly, and practices that involve remuneration intended to induce prescribing, purchases, or recommendations may be subject to scrutiny if they do not qualify for an exemption or safe harbor.

Federal false claims laws prohibit any person from knowingly presenting, or causing to be presented, a false claim for payment to the federal government, or knowingly making, or causing to be made, a false statement to have a false claim paid. This includes claims made to programs where the federal government reimburses, such as Medicaid, as well as programs where the federal government is a direct purchaser, such as when it purchases off the Federal Supply Schedule. Recently, several pharmaceutical and other healthcare companies have been prosecuted under these laws for allegedly inflating drug prices they report to pricing services, which in turn were used by the government to set Medicare and Medicaid reimbursement rates, and for allegedly providing free product to customers with the expectation that the customers would bill federal programs for the product. In addition, certain marketing practices, including off-label promotion, may also violate false claims laws. Additionally, PPACA amended the healthcare program anti-kickback statute such that a violation can serve as a basis for liability under the federal false claims law. The majority of states also have statutes or regulations similar to the federal anti-kickback law and false claims laws, which apply to items and services reimbursed under Medicaid and other state programs, or, in several states, apply regardless of the payor.

The U.S. federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, created additional federal criminal statutes that prohibit among other actions, knowingly and willfully executing, or attempting to execute, a scheme to defraud any healthcare benefit program, including private third-party payors or making any false, fictitious or fraudulent statement in connection with the delivery of or payment for healthcare benefits, items or services. HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act of 2009, or HITECH, and their implementing regulations, impose obligations on certain types of individuals and entities regarding the electronic exchange of information in common healthcare transactions, as well as standards relating to the privacy and security of individually identifiable health information.i

Other federal statutes pertaining to healthcare fraud and abuse include the civil monetary penalties statute, which prohibits the offer or payment of remuneration to a Medicaid or Medicare beneficiary that the offeror/payor knows or should know is likely to influence the beneficiary to order a receive a reimbursable item or service from a particular supplier, and the healthcare fraud statute, which prohibits knowingly and willfully executing or attempting to execute a scheme to defraud any healthcare benefit program or obtain by means of false or fraudulent pretenses, representations, or promises any money or property owned by or under the control of any healthcare benefit program in connection with the delivery of or payment for healthcare benefits, items, or services.

Additionally, to the extent that our product is sold in a foreign country, we may be subject to similar foreign laws.

Privacy and Security laws

HIPAA, as amended by HITECH, and their respective implementing regulations, impose privacy, security transmission and breach reporting obligations with respect to individually identifiable health information, including protected health information, or PHI, upon entities subject to the law, such as health plans, healthcare clearinghouses and certain healthcare providers, and their respective business associates that perform services on their behalf that involve individually identifiable health information, including PHI. HIPAA imposes criminal liability and amends provisions on the reporting, investigation, enforcement, and penalizing of civil liability for, among other things, knowingly and recklessly executing a scheme or artifice to defraud any healthcare benefit program, including private payors, as well as knowingly and willfully falsifying, concealing, or covering up a material fact by any trick, scheme, or device or making any materially false, fictitious, or fraudulent statement in connection with the delivery of or payment for healthcare benefits, items, or services. A violation of this statute is a felony and may result in fines, imprisonment, or exclusion from government-sponsored programs. Similar to the federal Anti-Kickback Statute, a person or entity no longer needs to have actual knowledge of this statute or specific intent to violate it in order to have committed a violation. In addition, state attorney generals have authority to file civil actions for damages or injunctions in federal courts to enforce the HIPAA laws and seek attorneys' fees and costs associated with pursuing federal civil actions. Although we are not directly subject to HIPAA, other than potentially with respect to providing certain employee benefits, we could be subject to criminal penalties if we knowingly obtain or disclose individually identifiable health information maintained by a HIPAA covered entity in a manner that is not authorized or permitted by HIPAA.

Many states have laws that protect the privacy and security of sensitive and personal information, including health information, to which we are subject. For example, California enacted the California Consumer Privacy Act, or CCPA, which creates individual privacy rights for California consumers and increases the privacy and security obligations of entities handling certain personal data. The CCPA became effective on January 1, 2020. The CCPA provides for civil penalties for violations, as well as a private right of action for data breaches that is expected to increase data breach litigation.

Federal and state laws that govern the privacy and security of health information or personally identifiable information in certain circumstances, including state health information privacy and data breach notification laws which govern the collection, use, disclosure, and protection of health-related and other personal information, many of which differ from each other in significant ways, may require us to undertake compliance efforts that could be costly and time consuming or subject us to liability for a failure to comply.

Other Federal and State Regulatory Requirements

Manufacturers of prescription drugs are required to collect and report information on certain payments or transfers of value to physicians and teaching hospitals, as well as investment interests held by physicians and their immediate family members. The reports must be submitted on an annual basis and the reported data are posted in searchable form on a public website on an annual basis. Failure to submit required information may result in civil monetary penalties. Effective January 1, 2022, transfers of value to physician assistants, nurse practitioners or clinical nurse specialists, certified registered nurse anesthetists, and certified nurse-midwives will also be required.

In addition, several states now require prescription drug companies to report certain expenses relating to the marketing and promotion of drug products and to report gifts and payments to individual healthcare practitioners in these states. Other states prohibit various marketing-related activities, such as the provision of certain kinds of gifts or meals. Still other states require the posting of information relating to clinical studies and their outcomes. Some states require the reporting of certain pricing information, including information pertaining to and justifying price increases, or prohibit prescription drug price gouging. In addition, states such as California, Connecticut, Nevada and Massachusetts require pharmaceutical companies to implement compliance programs and/or marketing codes. Additional jurisdictions, such as the City of Chicago and the District of Columbia, require pharmaceutical sales representatives to be licensed and meet continuing education requirements. Several additional states are considering similar proposals. Compliance with these laws is difficult and time-consuming, and companies that do not comply with these state laws face civil penalties.

Healthcare Reform

The U.S. and many foreign jurisdictions have enacted or proposed legislative and regulatory changes affecting the healthcare system. The U.S. government, state legislatures and foreign governments also have shown significant interest in implementing cost-containment programs to limit the growth of government-paid healthcare costs, including price controls, restrictions on reimbursement and requirements for substitution of generic products for branded prescription drugs.

In recent years, Congress has considered reductions in Medicare reimbursement levels for drugs administered by physicians. CMS, the agency that administers the Medicare and Medicaid programs, also has authority to revise reimbursement rates and to implement coverage restrictions for some drugs. Cost reduction initiatives and changes in coverage implemented through legislation or regulation could decrease utilization of and reimbursement for any approved products. While Medicare regulations apply only to drug benefits for Medicare beneficiaries, private payers often follow Medicare coverage policy and payment limitations in setting their own reimbursement rates. Therefore, any reduction in reimbursement that results from federal legislation or regulation may result in a similar reduction in payments from private payers.

The Patient Protection and Affordable Care Act, as amended by the Health Care and Education Affordability Reconciliation Act, or collectively the Affordable Care Act, substantially changed the way healthcare is financed by both governmental and private insurers, and significantly impacts the pharmaceutical industry. The Affordable Care Act is intended to broaden access to health insurance, reduce or constrain the growth of healthcare spending, enhance remedies against healthcare fraud and abuse, add new transparency requirements for healthcare and health insurance industries, impose new taxes and fees on pharmaceutical and medical device manufacturers, and impose additional health policy reforms. Among other things, the Affordable Care Act expanded manufacturers' rebate liability under the Medicaid Drug Rebate Program by increasing the minimum Medicaid rebate for both branded and generic drugs, expanded the 340B program, and revised the definition of AMP, which could increase the amount of Medicaid drug rebates manufacturers are required to pay to states. The legislation also extended Medicaid drug rebates, previously due only on fee-for-service Medicaid utilization, to include the utilization of Medicaid managed care organizations as well and created an alternative rebate formula for certain new formulations of certain existing products that is intended to increase the amount of rebates due on those drugs. On February 1, 2016, CMS issued final regulations to implement the changes to the Medicaid Drug Rebate program under the Affordable Care Act. These regulations became effective on April 1, 2016. Since that time, there have been significant ongoing efforts to modify or eliminate the Affordable Care Act.

There have been significant ongoing efforts to modify or eliminate the Affordable Care Act. For example, the Tax Act, enacted on December 22, 2017, repealed the shared responsibility payment for individuals who fail to maintain minimum essential coverage under section 5000A of the Internal Revenue Code of 1986, as amended, or the Code, commonly referred to as the individual mandate.

Other legislative changes have been proposed and adopted since passage of the Affordable Care Act. The Budget Control Act of 2011, among other things, created the Joint Select Committee on Deficit Reduction to recommend proposals in spending reductions to Congress. The Joint Select Committee did not achieve its targeted deficit reduction of an amount greater than $1.2 trillion for the fiscal years 2012 through 2021, triggering the legislation's automatic reductions to several government programs. These reductions included aggregate reductions to Medicare payments to healthcare providers of up to 2.0% per fiscal year, which went into effect in April 2013. Subsequent litigation extended the 2% reduction, on average, to 2030 unless additional Congressional action is taken. However, pursuant to the Coronavirus Aid, Relief and Economic Security Act, or CARES Act, the 2% Medicare sequester reductions were suspended from May 1, 2020 through December 31, 2021 due to the COVID-19 pandemic. On January 2, 2013, the American Taxpayer Relief Act was signed into law, which, among other things, reduced Medicare payments to several types of providers, including hospitals, imaging centers and cancer treatment centers, and increased the statute of limitations period for the government to recover overpayments to providers from three to five years.

The Affordable Care Act has been subject to challenges in the courts. On December 14, 2018, a Texas U.S. District Court Judge ruled that the Affordable Care Act is unconstitutional in its entirety because the "individual mandate" was repealed by Congress. On December 18, 2019, the Fifth Circuit U.S. Court of Appeals held that the individual mandate is unconstitutional and remanded the case to the Texas District Court to reconsider its earlier invalidation of the entire Affordable Care Act. An appeal was taken to the U.S. Supreme Court which heard oral arguments in the case on November 10, 2020. On June 17, 2021, the Supreme Court ruled that the plaintiffs lacked standing to challenge the law as they had not alleged personal injury traceable to the allegedly unlawful conduct. As a result, the Supreme Court did not rule on the constitutionality of the Affordable Care Act or any of its provisions.

The Affordable Care Act requires pharmaceutical manufacturers of branded prescription drugs to pay a branded prescription drug fee to the federal government. Each individual pharmaceutical manufacturer pays a prorated share of the branded prescription drug fee, based on the dollar value of its branded prescription drug sales to certain federal programs identified in the law. Furthermore, the law requires manufacturers to provide a 50% discount off the negotiated price of prescriptions filled by beneficiaries in the Medicare Part D coverage gap, referred to as the "donut hole." The Bipartisan Budget Act of 2018, among other things, amended the Affordable Care Act, effective January 1, 2019, to close the coverage gap in most Medicare drug plans by increasing from 50% to 70% the point-of-sale discount that is owed by pharmaceutical manufacturers who participate in Medicare Part D.

The Affordable Care Act also expanded the Public Health Service's 340B drug pricing program. As noted above, the 340B drug pricing program requires participating manufacturers to agree to charge statutorily-defined covered entities no more than the 340B "ceiling price" for the manufacturer's covered outpatient drugs. The Affordable Care Act expanded the 340B program to include additional types of covered entities: certain free-standing cancer hospitals, critical access hospitals, rural referral centers and sole community hospitals, each as defined by the Affordable Care Act. Because the 340B ceiling price is determined based on AMP and Medicaid drug rebate data, revisions to the Medicaid rebate formula and AMP definition could cause the required 340B discounts to increase.

Payment methodologies may be subject to changes in healthcare legislation and regulatory initiatives as well. For example, CMS may develop new payment and delivery models, such as bundled payment models. Recently, there has been heightened governmental scrutiny over the manner in which manufacturers set prices for their marketed products. Such scrutiny has resulted in several recent U.S. Congressional inquiries and proposed and enacted federal and state legislation designed to, among other things, bring more transparency to drug pricing, review the relationship between pricing and manufacturer patient programs, reduce the cost of drugs under Medicare, and reform government program reimbursement methodologies for pharmaceutical products.

Further changes to and under the Affordable Care Act remain possible, but it is unknown what form any such changes or any law proposed to replace or revise the Affordable Care Act would take, and how or whether it may affect our business in the future.

At the state level, legislatures have increasingly passed legislation and implemented regulations designed to control pharmaceutical product pricing, including price or patient reimbursement constraints, discounts, restrictions on certain product access and marketing cost disclosure and transparency measures, and, in some cases, designed to encourage importation from other countries and bulk purchasing.

We expect that additional federal, state and foreign healthcare reform measures will be adopted in the future, any of which could limit the amounts that federal and state governments will pay for healthcare products and services, which could result in limited coverage and reimbursement and reduced demand for our products, once approved, or additional pricing pressures.

Foreign Corrupt Practices Act

The Foreign Corrupt Practices Act, or FCPA, prohibits U.S. businesses and their representatives from offering to pay, paying, promising to pay or authorizing the payment of money or anything of value to a foreign official in order to influence any act or decision of the foreign official in his or her official capacity or to secure any other improper advantage in order to obtain or retain business. The FCPA also obligates companies whose securities are listed in the U.S. to comply with accounting provisions requiring us to maintain books and records, which in reasonable detail, accurately and fairly reflect the transactions and dispositions of the assets of the corporation, including international subsidiaries, if any, and to devise and maintain a system of internal accounting controls sufficient to provide reasonable assurances regarding the reliability of financial reporting and the preparation of financial statements. Our industry is heavily regulated and therefore involves significant interaction with public officials, including officials of non-U.S. governments. Additionally, in many other countries, the health care providers who prescribe pharmaceuticals are employed by their government, and the purchasers of pharmaceuticals are government entities; therefore, our dealings with these prescribers and purchasers are subject to regulation under the FCPA. Recently, the Securities and Exchange Commission, or the SEC, and Department of Justice have increased their FCPA enforcement activities with respect to pharmaceutical companies. Violations could result in fines, criminal sanctions against us, our officers, or our employees, the closing down of our facilities, requirements to obtain export licenses, cessation of business activities in sanctioned countries, implementation of compliance programs, and prohibitions on the conduct of our business. Recent enacted legislation has expanded the SEC's power to seek disgorgement in all FCPA cases filed in federal court and extended the statute of limitations in SEC enforcement actions in intent-based claims such as those under the FCPA from five years to ten years.

International laws

In Europe, and throughout the world, other countries have enacted anti-bribery laws and/or regulations similar to the FCPA. Violations of any of these antibribery laws, or allegations of such violations, could have a negative impact on our business, results of operations and reputation. There are also international privacy laws that impose restrictions on the access, use, including the EU's General Data Protection Regulation, and disclosure of health information. All of these laws may impact our business. Our failure to comply with these privacy laws or significant changes in the laws restricting our ability to obtain required patient information could significantly impact our business and our future business plans.

CVie Acquisition

In December 2018, we acquired CVie Investments Limited, or CVie Investments, an exempted company with limited liability incorporated under the laws of the Cayman Islands, which we refer to herein as the CVie Acquisition. Since the CVie Acquisition, we have operated CVie Investments and its wholly owned subsidiary, CVie Therapeutics Limited, or CVie Therapeutics, a Taiwan corporation organized under the laws of the Republic of China, as a subsidiary focused on the development of drug product candidates for cardiovascular diseases.

Employees and Human Capital Resources

As of March 31, 2022, we have 33 full-time employees, 28 of whom are based in the U.S. Our employees are skilled in drug and device development, including clinical trial design, clinical operations in support of our clinical trials and related activities, corporate administration, finance and business development. None of our employees are represented by a labor union or covered by collective bargaining agreements, and we believe our relationship with our employees is good. We also work with independent professional advisors and consultants to support our program development activities, particularly in the areas of drug product development, regulatory, compliance, and international clinical operations.

We believe our human capital resources are fundamental to our success; as such, our corporate objectives include recruiting, retaining, incentivizing and integrating existing and new employees, advisors and consultants for the common purpose of increasing stockholder value and promoting the success of our company. Our compensation and equity incentive programs are designed to attract, retain and reward personnel through cash-based compensation and granting of stock-based awards intended to motivate such individuals to perform to the best of their abilities and advance our corporate objectives. We endeavor to provide competitive benefits that will reward and retain our employees. Our compensation program includes competitive salary and annual bonus programs, comprehensive healthcare benefits for employees and dependent family members, paid time off, paid holidays, family medical leave and flexible work schedules. We sponsor a 401(k) plan and automatically enroll all employees when eligible and generally provide a discretionary matching corporate contribution. In response to the COVID-19 pandemic, we implemented significant changes that we determined were in the best interest of our employees and our company, and which complied with government regulations. This included initially providing all employees the option of working from home, while implementing additional workplace safety measures for employees working on site.

Corporate Information

We were incorporated in Delaware on November 6, 1992. Our principal executive offices are located at 2600 Kelly Road, Suite 100, Warrington, Pennsylvania, 18976, and our telephone number is 215-488-9300. Our website address is www.windtreetx.com. The information contained in, or accessible through, our website does not constitute part of this Annual Report on Form 10-K. We have included our website address as an inactive textual reference only.

Available Information

We file annual, quarterly and current reports, proxy or stockholder information statements and other information with the SEC. The SEC maintains an Internet site that contains reports, proxy and information statements, certain and other information that we may file electronically with the SEC (http://www.sec.gov). We maintain our corporate website at http://www.windtreetx.com. Our website and the information contained therein or connected thereto are not incorporated into this Annual Report on Form 10-K.

ITEM 1A. RISK FACTORS.

You should carefully consider the following risks and uncertainties when reading this Annual Report on Form 10-K. If any of the following risks actually occurs, our business, financial condition and results of operations could be materially and adversely affected. In that event, the trading price of our common stock could decline. Although we believe that we have identified and discussed below the key risk factors affecting our business, there may be additional risks and uncertainties that are not presently known or that are not currently believed to be significant that may adversely affect our performance or financial condition.

Risks Related to Our Financial Condition

We have incurred significant operating losses since inception, we expect to incur operating losses in the future, and we may not be able to achieve or sustain profitability.

We have incurred operating losses since our incorporation on November 6, 1992. For the years ended December 31, 2021 and 2020, we had operating losses of $77.3 million and $30.3 million, respectively. As of December 31, 2021, we had an accumulated deficit of $785.3 million. To date, we have financed our operations primarily through private placements and public offerings of our common and preferred stock and borrowings from investors and financial institutions.

We expect to continue to incur significant research and clinical development, regulatory and other expenses as we (i) continue to develop our product candidates; (ii) seek regulatory clearances or approvals for our planned or future product candidates; (iii) conduct clinical trials on our existing and planned or future product candidates; and (iv) manufacture, market and sell any product candidates for which we may obtain regulatory approval. As a result, we expect to continue to incur operating losses for the foreseeable future and may never achieve profitability. Even if we do achieve profitability, we may not be able to sustain or increase profitability on an ongoing basis. If we do not achieve or sustain profitability, it will be more difficult for us to finance our business and accomplish our strategic objectives, either of which would have a material adverse effect on our business, financial condition and results of operations and may cause the market price of our common stock to decline.

Our losses, negative cash flows from operations, and accumulated deficit raise substantial doubt about our ability to continue as a going concern absent obtaining adequate new debt or equity financings.

Management has concluded that substantial doubt exists about our ability to continue as a going concern for the next twelve months from the date of the financial statements included in this Annual Report on Form 10-K. As of December 31, 2021, we had cash and cash equivalents of $22.3 million and current liabilities of $4.9 million. As of March 31, 2022, we believe that we have sufficient resources available to support our development activities and business operations and satisfy our obligations into the first quarter of 2023. We do not have sufficient cash and cash equivalents as of the date of this Annual Report on Form 10-K to support our operations for at least the 12 months following the date that the financial statements are issued.

To alleviate the conditions that raise substantial doubt about our ability to continue as a going concern, management plans to secure additional capital, potentially through a combination of public or private equity offerings and strategic transactions, including potential licensing arrangements, alliances and drug product collaborations focused on specified geographic markets; however, none of these alternatives are committed at this time. There can be no assurance that we will be successful in obtaining sufficient funding on terms acceptable to us to fund continuing operations, if at all, or identify and enter into any strategic transactions that will provide the capital that we will require. If none of these alternatives is available, or if available, we are unable to raise sufficient capital through such transactions, we will not have sufficient cash resources and liquidity to fund our business operations for at least the next 12 months following the date that the financial statements are issued. The failure to obtain sufficient capital on acceptable terms when needed may require us to delay, limit, or eliminate the development of business opportunities and our ability to achieve our business objectives and our competitiveness, and our business, financial condition, and results of operations will be materially adversely affected. In addition, market instability, including as a result of the ongoing COVID-19 pandemic and geopolitical instability, may reduce our ability to access capital, which could negatively affect our liquidity and ability to continue as a going concern. In addition, the perception that we may not be able to continue as a going concern may cause others to choose not to deal with us due to concerns about our ability to meet our contractual obligations.

The report of our independent registered accounting firm on our audited financial statements for the fiscal year ended December 31, 2021 contains an explanatory paragraph relating to our ability to continue as a going concern.

The auditor's opinion on our audited financial statements for the year ended December 31, 2021 includes an explanatory paragraph stating that we have incurred recurring losses from operations that raise substantial doubt about our ability to continue as a going concern. While we believe that we will be able to raise the capital we need to continue our operations, there can be no assurances that we will be successful in these efforts or will be able to resolve our liquidity issues or eliminate our operating losses. If we are unable to obtain sufficient funding, we would need to significantly reduce our operating plans and curtail some or all of our development efforts. Accordingly, our business, prospects, financial condition, and results of operations will be materially and adversely affected, and we may be unable to continue as a going concern. If we seek additional financing to fund our business activities in the future and there remains substantial doubt about our ability to continue as a going concern, investors or other financing sources may be unwilling to provide additional funding on commercially reasonable terms or at all.

We will require substantial additional financing to achieve our goals, and a failure to obtain this necessary capital when needed on acceptable terms, or at all, could force us to delay, limit, reduce or terminate our product development programs, or other operations.

The development of biopharmaceutical product candidates is capital-intensive. We expect our expenses to increase in connection with our ongoing activities, particularly as we conduct our ongoing and planned clinical trials under our key clinical development programs, continue research and development and potentially initiate clinical trials under our other development programs and seek regulatory approval for our current product candidates and any future product candidates we may develop. In addition, as our product candidates progress through development and toward commercialization, we may need to make milestone payments to licensors and other third parties from whom we have in-licensed or acquired our product candidates. Furthermore, if and to the extent we seek to acquire or in-license additional product candidates in the future, we may be required to make significant upfront payments, milestone payments, and/or licensing payments. If we obtain regulatory approval for any of our product candidates, we also expect to incur significant commercialization expenses related to product manufacturing, marketing, sales and distribution. Because the outcome of any clinical trial or preclinical study is highly uncertain, we cannot reasonably estimate the actual amounts necessary to successfully complete the development and commercialization of our product candidates. Accordingly, we will need to obtain substantial additional funding in connection with our continuing operations. Moreover, a small group of investors that hold a significant portion of our issued and outstanding common stock may be in a position to influence the terms of a funding transaction, potentially making it more difficult to reach agreement on terms that are acceptable to investors participating in the financing, in a timely manner, if at all. If we are unable to raise sufficient capital to fund our activities when needed and on acceptable terms, we could be forced to delay, reduce or eliminate our research and development programs or, if our product candidates are approved, any future commercialization efforts.

Our existing cash and cash equivalents are not sufficient to fund operations for at least the next 12 months. We currently do not have sufficient capital to execute our planned phase 2 clinical trial of istaroxime for the treatment of AHF. We are exploring capital from public and private equity offerings and potential strategic opportunities to fund the initiation of this clinical trial, and plan to execute the clinical trial after obtaining adequate funding.

We have based estimates included in our operating plan on assumptions that may prove to be wrong, and we could use our capital resources sooner than we currently expect. Our operating plans and other demands on our cash resources may change as a result of many factors currently unknown to us, and we may need to seek additional funds sooner than planned, through public or private equity or debt financings or other capital sources, including potentially collaborations, licenses and other similar arrangements. In addition, we may seek additional capital due to favorable market conditions or strategic considerations even if we believe we have sufficient funds for our current or future operating plans. Attempting to secure additional financing may divert our management from our day-to-day activities, which may adversely affect our ability to develop our product candidates.

Our future capital requirements will depend on many factors, including:

- the type, number, scope, progress, expansions, results, costs and timing of our clinical trials and preclinical studies of our product candidates, which we are pursuing or may choose to pursue in the future;
- the costs and timing of manufacturing for our product candidates, including commercial manufacturing if any product candidate is approved;
- the costs, timing and outcome of regulatory review of our product candidates;

- the costs of obtaining, maintaining and enforcing our patents and other intellectual property rights;
- the timing and amount of the milestone or other payments we must make to the licensors and other third parties from whom we have in-licensed or acquired our product candidates;
- the costs and timing of establishing or securing sales and marketing capabilities if any product candidate is approved;
- the costs, terms and timing of establishing and maintaining collaborations, licenses and other similar arrangements;
- costs associated with any product candidates or technologies that we may in-license or acquire; and
- our ability to achieve sufficient market acceptance, coverage and adequate reimbursement from payors and adequate market share and revenue for any approved products.

Conducting clinical trials and preclinical studies is a time consuming, expensive and uncertain process that takes years to complete, and we may never generate the necessary data or results required to obtain regulatory approval and achieve product sales. In addition, our product candidates, if approved, may not achieve commercial success.

Accordingly, we will need to continue to rely on additional financing to achieve our business objectives. Adequate additional financing may not be available to us at any time on acceptable terms, or at all.

Raising additional capital may cause dilution to our stockholders, restrict our operations or require us to relinquish rights to our technologies or product candidates.

Until we can generate substantial product revenues to support our operations, we expect to finance our cash needs through equity offerings, debt financings or other capital sources, including potentially collaborations, licenses and other strategic transactions. This may include equity sales pursuant to an at-the-market offering agreement which allows us to offer and sell, from time to time at our sole discretion, up to a maximum of $10.0 million of shares of our common stock under an at-the-market program, or the ATM Program. To the extent that we raise additional capital through the sale of equity or convertible debt securities, our stockholders' ownership interests will be diluted, and the terms of these securities may include liquidation or other preferences that adversely affect their rights as common stockholders. Debt financing and preferred equity financing, if available, may involve agreements that include covenants limiting or restricting our ability to take specific actions, such as incurring additional debt, making capital expenditures or declaring dividends.

If we raise funds through future collaborations, licenses and other similar arrangements, we may have to relinquish valuable rights to our future revenue streams, research programs or product candidates or grant licenses on terms that may not be favorable to us and/or that may reduce the value of our common stock.

Unstable market and economic conditions may have serious adverse consequences on our business, financial condition, and stock price.

Global financial markets have recently, and may continue to, experience extreme volatility and disruptions, declines in consumer confidence, declines in economic growth, increases in unemployment rates, and uncertainty about economic stability as a result of the ongoing COVID-19 pandemic, political unrest, and other factors beyond control. There can be no assurance that further deterioration in credit and financial markets and confidence in economic conditions will not occur. Our general business strategy and ability to raise capital may be adversely affected by any such economic downturn, volatile business environment, or continued unpredictable and unstable market conditions. If the current equity and credit markets deteriorate, it may make any necessary debt or equity financing more difficult, more costly, and more dilutive. Failure to secure any necessary financing in a timely manner and on favorable terms could have a material adverse effect on our growth strategy, financial performance, and stock price and could require us to delay or abandon clinical development plans. In addition, there is a risk that one or more of our current service providers, manufacturers, and other partners may not survive these difficult economic times, which could directly affect our ability to attain our operating goals on schedule and on budget.

In addition, the stock markets have experienced extreme price and volume fluctuations that have affected and continue to affect the market prices of equity securities of many companies, including in connection with the ongoing COVID-19 pandemic, which has resulted in decreased stock prices for many companies notwithstanding the lack of a fundamental change in their underlying business models or prospects. These fluctuations have often been unrelated or disproportionate to the operating performance of those companies. Further, the impacts of political unrest, including as a result geopolitical tension, such as a deterioration in the relationship between the U.S. and China or continued escalation in conflict between Russia and Ukraine, including any additional sanctions, export controls or other restrictive actions that may be imposed by the U.S. and/or other countries against governmental or other entities in, for example, China or Russia, also could lead to disruption, instability, and volatility in the global markets, which may have an adverse impact on our business or ability to access the capital markets. Broad market and industry factors, including potentially worsening economic conditions and other adverse effects, or developments relating to the ongoing COVID-19 pandemic, political, regulatory, and other market conditions, may negatively affect the market price of shares of our common stock, regardless of our actual operating performance.

Due to the significant resources required to develop each of our product candidates, we must prioritize development of certain product candidates and/or certain disease indications. We may be delayed in advancing a product candidate if our plan does not include sufficient funding to execute a clinical program. If we expend our limited resources on candidates or indications that do not yield a successful product and fail to capitalize on other product candidates or indications that may be more profitable or for which there is a greater likelihood of success, such failure could have a material adverse effect on our business, financial condition, results of operations, and prospects.

We are currently focused on developing product candidates to address unmet medical needs in acute cardiovascular and pulmonary diseases. We seek to allocate our limited capital among our programs in an efficient manner and to advance our cardiovascular product candidate. However, due to the significant resources required to advance the development of our product candidates, we also must focus on specific diseases and disease pathways and decide which product candidates to pursue and the amount of resources to allocate to each such product candidate.

Our ability to advance a product candidate depends on our ability to secure the additional capital required to execute each phase of product development. In developing our plan, we were aware of the size and projected costs of our planned phase 2b clinical trial in istaroxime to improve cardiac functions in patients with AHF and determined to allocate our limited resources to other programs. Such decisions concerning the allocation of research and development funds towards, or away from, particular product candidates or therapeutic areas may not lead to the development of any viable commercial product and may divert resources away from better opportunities. Similarly, any decision to delay, terminate or engage with third parties in respect of certain programs may subsequently also prove to be suboptimal and could cause us to miss valuable opportunities. In that event, our business, financial condition and results of operations could be materially adversely affected. As a result, we may fail to capitalize on viable commercial products or profitable market opportunities, be required to forego or delay pursuit of opportunities with other product candidates or other diseases and disease pathways that may later prove to have greater commercial potential than those we choose to pursue, or relinquish valuable rights to such product candidates through collaboration, licensing or other royalty arrangements in cases in which it would have been advantageous for us to invest additional resources to retain development and commercialization rights.

We may never realize the full value of our intangible assets.

We have recorded significant goodwill and intangible assets on our consolidated balance sheets as a result of the acquisition of CVie Therapeutics in December 2018. The identifiable intangible assets resulting from the CVie Therapeutics acquisition relate to IPR&D of istaroxime and rostafuroxin. In accordance with applicable accounting standards, we are required to review intangible assets and goodwill for impairment on an annual basis, or more frequently where there is an indication of impairment. During the second quarter of 2021, we concluded an initial process to test the industry's interest in investing in our rostafuroxin drug candidate and were not able to secure a licensing transaction or other strategic opportunity at that time. Based on feedback received from potential licensing partners, we determined that there is a need for an additional phase 2 clinical trial to demonstrate efficacy in non-Caucasian patients in treatment resistant hypertension. Due to these developments, we determined that the fair value of the IPR&D related to our rostafuroxin drug candidate was more likely than not less than its carrying value. As a result, we recorded a loss on impairment of intangible assets of $37.8 million during the second quarter of 2021. As part of our annual quantitative impairment assessment of indefinite-lived IPR&D intangible assets, we reassessed certain of the assumptions related to our rostafuroxin drug candidate due to the current macroeconomic conditions which have made it harder to secure the funding needed to conduct the additional phase 2 clinical trial and have therefore delayed our intended development of rostafuroxin. As a result, we concluded that the fair value of the IPR&D related to our rostafuroxin drug candidate was again less than its carrying value and recorded an additional loss on impairment of intangible assets of $7.2 million during the fourth quarter of 2021. No events or changes in the business environment occurred during 2021 that would indicate that the fair value of the IPR&D related to our istaroxime drug candidate or our goodwill was impaired. We are continuing to pursue licensing arrangements and/or other strategic partnerships for rostafuroxin. However, if we are unable to secure such an arrangement or partnership, or if we secure an arrangement for an amount less than anticipated, we may have to record additional impairments related to rostafuroxin in the future, which may materially adversely affect our results of operations and financial condition.

If we fail to maintain proper and effective internal control over financial reporting, our ability to produce accurate and timely financial statements could be impaired, investors may lose confidence in our financial reporting and the trading price of our common stock may decline.

Pursuant to Section 404 of the Sarbanes-Oxley Act of 2002, as amended, we are required to furnish a report by our management on our internal control over financial reporting. We cannot assure you that there will not be material weaknesses or significant deficiencies in our internal control over financial reporting in the future. Any failure to maintain internal control over financial reporting could severely inhibit our ability to accurately report our financial condition, results of operations or cash flows. If our financial statements are not accurate, investors may not have a complete understanding of our operations. If we do not file our financial statements on a timely basis as required by the Securities and Exchange Commission, or the SEC, we could face severe consequences. If we are unable to conclude that our internal control over financial reporting is effective, investors may lose confidence in the accuracy and completeness of our financial reports, the market price of our common stock could decline, and we could be subject to sanctions or investigations by the Nasdaq Stock Market LLC, the SEC or other regulatory authorities. Moreover, responding to such investigations, are likely to consume a significant amount of our management resources and cause us to incur significant legal and accounting expense. Failure to remedy any material weakness in our internal control over financial reporting, or to maintain effective control systems, could also restrict our future access to the capital markets. This could result in an adverse reaction in the financial markets due to a loss of confidence in the reliability of our financial statements.

Risks Related to our Development Activities and Regulatory Approval of our Product Candidates

We are substantially dependent on the success of our lead product candidate istaroxime. To the extent that our clinical development of istaroxime is not successful, our business, financial condition, and results of operations may be materially adversely affected and the price of our common stock may decline.

We currently have no product candidates approved for sale, and we may never be able to develop marketable products. We are focusing a significant portion of our activities and resources on our lead product candidate, istaroxime, and we believe our prospects are highly dependent on, and a significant portion of the value of our company relates to, our ability to successfully obtain regulatory approval for istaroxime. The clinical development and regulatory approval of istaroxime is subject to many risks, including the risks discussed in other risk factors, and istaroxime may not receive marketing approval from any regulatory agency. If the results or timing of regulatory filings, the regulatory process, regulatory developments, clinical trials or preclinical studies, or other activities, actions or decisions related to istaroxime do not meet our or others' expectations, the market price of our common stock could decline significantly. Should the results of our clinical development program be insufficient to support regulatory approval, we may be forced to rely on our other product candidates, which will require additional time and resources to obtain regulatory approval. There can be no assurance that we will be able to successfully develop istaroxime.

Clinical development involves a lengthy and expensive process with an uncertain outcome, and results of preclinical studies and early clinical trials are not necessarily predictive of future results. In addition, our assumptions about why certain of our product candidates are worthy of future development and potential approval are based on data primarily collected by other companies. Our product candidates may not have favorable results in later clinical trials, if any, or receive regulatory approval on a timely basis, if at all.

Clinical drug development is expensive and can take many years to complete, and its outcome is inherently uncertain. We cannot guarantee that any clinical trials will be conducted as planned or completed on schedule, if at all, and failure can occur at any time during the preclinical study or clinical trial process as a result of inadequate study design, inadequate performance of a drug, inadequate adherence by patients or investigators to clinical trial protocols, or other factors. For example, conducting a toxicology study as part of the preclinical program for istaroxime, to be included in a required regulatory submission, could result in unanticipated findings that could potentially negatively impact the ongoing clinical program for istaroxime. In addition, there is not data currently available to show the impact of istaroxime on early cardiogenic shock. Despite promising preclinical or clinical results,

any product candidate can unexpectedly fail at any stage of preclinical or clinical development. The historical failure rate for product candidates in our industry is high.

New drugs in later stages of clinical trials may fail to show the desired safety and efficacy traits despite having progressed through earlier clinical trials. As a result, data we obtain from our phase 2 clinical trials may not accurately predict phase 3 trial results, whether due to differences in sample size, study arms, duration, endpoints, or other factors. If any of our product candidates should fail to perform as designed in their respective phase 3 clinical programs, such failures could adversely affect the results of our clinical development program despite promising results in earlier trials. If clinical trials for any of our product candidates fail to demonstrate safety or efficacy to the satisfaction of the U.S. Food and Drug Administration, or FDA, or the equivalent regulatory authorities in other countries, the FDA or the equivalent regulatory authorities in other countries will not approve that drug and we would not be able to commercialize it, which could have a material adverse effect on our business, financial condition, results of operations, and prospects. Moreover, if we are required to cease development activities on any of our recently acquired product candidates due to adverse clinical results or otherwise, it could result in impairment of related intangible assets and goodwill on our consolidated balance sheets.

Even if later stage clinical trials are successful, regulatory authorities may question the trial design or sufficiency for approval of the endpoints we select for our clinical trials or add new requirements, such as the completion of additional studies, as conditions for obtaining approval or obtaining an indication. For the foregoing reasons, we cannot be certain that our ongoing and planned clinical trials and preclinical studies will be successful. Any safety concerns observed in any one of our clinical trials in our targeted indications could limit the prospects for regulatory approval of our product candidates in those and other indications, which could have a material adverse effect on our business, financial condition and results of operations, and result in significant additional costs and expenses, require additional time and have an adverse effect on our business, including our financial condition and results of operations.

We have limited experience with the development of therapies targeted to the treatment of early cardiogenic shock and COVID-19-related acute lung injury and may not succeed in our efforts to gain approval of our product candidates and establish a profitable business.

Although our team has significant experience with designing and conducting clinical trials, and has access to data, preclinical work and research conducted by our predecessor concerning istaroxime and expertise in the development of cardiovascular product candidates generally and the treatment of AHF in particular, we have limited experience in conducting clinical trials through to regulatory approval for the treatment of early cardiogenic shock. In addition, while we believe that our KL4 surfactant may have the potential to be an effective intervention for influenza-induced acute lung injury, or ALI, and have previously conducted preclinical studies assessing the utility of KL4 surfactant in the treatment of influenza-induced ALI and, in 2009, conducted a clinical trial assessing our KL4 surfactant in young children after exposure to serious respiratory infections such as influenza (including the type A serotype referred to as H1N1) or respiratory syncytial virus, we do not have experience in conducting clinical trials through to regulatory approval of a product candidate for patients with COVID-19 associated lung injury. We also have not produced any prior clinical or preclinical data in these indications. In part because of this lack of precedent, we are subject to development risks associated with studying new indications and cannot be certain that such developments will be successful.

Delays in clinical trials are common and have many causes, and any delay could result in increased costs to us and jeopardize or delay our ability to obtain regulatory approval and commence product sales or allow for competition to emerge.

We may experience delays in clinical trials of our product candidates, or the time required to complete clinical trials for our product candidates may be longer than anticipated. Our planned clinical trials may not begin on time, have an effective design, enroll a sufficient number of patients, or be completed on schedule, if at all. Our clinical trials can be delayed for a variety of reasons, including, but not limited to:

- delays associated with severe acute respiratory syndrome coronavirus 2, or SARS-CoV-2, the causative agent in a novel strain of coronavirus, or COVID-19, which will impact our healthcare systems and our trial sites ability to conduct trials to varied degrees and times. COVID-19 creates risk of interrupting availability of necessary clinical supplies, local regulatory reviews, hospital ethics committee reviews, professional staff, site monitors and other necessary travel;
- our inability to raise funding necessary to initiate or continue a trial;
- delays in obtaining regulatory approval to commence a trial or reaching a consensus with regulatory authorities on trial design;
- delays in reaching an agreement with the FDA or the equivalent foreign regulatory authorities in other countries on final trial design or the scope of the development program;
- inability to develop studies that are acceptable in all markets of interest;
- inability to come to an agreement on clinical trial design or execution factors with potential development partners;
- imposition of a clinical hold following an inspection of our clinical trial operations or trial sites by the FDA or the equivalent regulatory authorities in other countries;
- failures or delays in reaching agreement on acceptable terms with prospective CROs and clinical trial sites, the terms of which can be subject to extensive negotiation and may vary significantly among different CROs and trial sites;
- delays in obtaining contracts with clinical sites and required IRB approval at each site;
- IRBs refusing to approve, suspending or terminating the trial at an investigational site, precluding enrollment of additional subjects, or withdrawing their approval of the trial;
- competition with other studies for study patients;
- changes to clinical trial protocol;
- delays in recruiting suitable patients to participate in a trial;

- subjects choosing an alternative treatment for the indication for which we are developing our product candidates, or participating in competing clinical trials;
- delays in having subjects complete participation in a trial or return for post-treatment follow-up;
- clinical sites deviating from trial protocol or dropping out of a trial to the detriment of enrollment;
- subjects experiencing severe or unexpected adverse events;
- occurrence of serious adverse events in trials of the same class of agents conducted by other companies;
- selection of clinical endpoints that require prolonged periods of clinical observation or analysis of the resulting data;
- third-party clinical investigators losing the licenses or permits necessary to perform our clinical trials, not performing our clinical trials on our anticipated schedule or consistent with the clinical trial protocol, GCPs, or other regulatory requirements;
- third-party contractors not performing data collection or analysis in a timely or accurate manner;
- third-party contractors becoming debarred or suspended or otherwise penalized by the FDA or other government or regulatory authorities for violations of regulatory requirements, in which case we may need to find a substitute contractor, and we may not be able to use some or all of the data produced by such contractors in support of our marketing applications;
- manufacturing sufficient quantities of product candidate or obtaining sufficient quantities of combination therapies for use in clinical trials or changes in the manufacturing process that may be necessary or desired;
- time required to add new clinical sites; or
- delays by our contract manufacturers to produce and deliver a sufficient supply of clinical trial materials or being ordered by the FDA or comparable foreign regulatory authorities to temporarily or permanently shut down due to violations of current good manufacturing practices, or cGMP, regulations or other applicable requirements, or infections or cross-contaminations of product candidates in the manufacturing process.

In addition, we may not reach agreement with the FDA, or a foreign regulator on the extent of our phase 3 programs, the design of any one or more of the clinical trials necessary for approval, or we may be unable to reach agreement on a single design that would permit us to conduct a common pivotal phase 3 clinical development program in all markets of interest. For example, we may not be able to design a study that is acceptable to both the FDA and European Medicines Agency, or EMA, regulators, which would cause us to limit the scope of our geographical activities or greatly increase our investment. Even if we complete the clinical trial within our anticipated time, if our results are inconclusive or non-compelling or otherwise insufficient to support a strategic or financing transaction, we potentially could be forced to limit or cease our development activities, which would have a material adverse effect on our business.

We have conducted, and may in the future conduct, clinical trials for our product candidates at clinical sites located in the U.S. and outside of the U.S. If the FDA and other foreign equivalents raise concerns about certain of the clinical sites based on location and regulatory environment, they may not accept data from such trials, in which case our development plans will be delayed, which could materially harm our business.

We have conducted and are expecting in the future to conduct one or more of our clinical trials for our product candidates at clinical sites located in the U.S. and outside of the U.S., including EU, China, Russia, and South America. Although the FDA may accept data from clinical trials conducted outside the U.S., acceptance of this data may be subject to certain conditions imposed by the FDA. For example, the FDA requires the clinical trial to have been conducted in accordance with GCPs, and the FDA must be able to validate the data from the clinical trial through an onsite inspection if it deems such inspection necessary. Where data from foreign clinical trials are intended to serve as the sole basis for marketing approval in the U.S., the FDA will not approve the application on the basis of foreign data alone unless those data are considered applicable to the U.S. patient population and U.S. medical practice, the clinical trials were performed by clinical investigators of recognized competence, and the data is considered valid without the need for an onsite inspection by the FDA or, if the FDA considers such an inspection to be necessary, the FDA is able to validate the data through an onsite inspection or other appropriate means. There can be no assurance the FDA will accept data from clinical trials conducted outside of the U.S. If the FDA does not accept data from our clinical trials of our product candidates, it would likely result in the need for additional clinical trials, which would be costly and time consuming and delay or permanently halt our development of our product candidates.

For example, we have previously conducted clinical trials in Russia, and may plan to do so again in the future. The escalation of tensions in the region, including Russia's February 2022 invasion of Ukraine and the resulting imposition of economic and other sanctions by the U.S., EU, and many other nations on Russia, individuals in Russia, Russian businesses, and the Russian central bank, could disrupt or delay our ability to conduct clinical trial activities in Russia in the future. Although the length and impact of any military action are highly unpredictable, clinical trial sites in Russia and other countries may close, and patients could be forced to evacuate or voluntarily choose to relocate far from clinical trial sites, making them unavailable for follow-up. The closure of sites, the inability to screen and enroll new patients or any premature discontinuation of treatment by patients enrolled in our future trials or our inability to conclude follow-up evaluations with patients that were enrolled in our completed clinical trial, could result in increased costs and could delay our anticipated timeline for the completion of our future clinical trials.

The COVID-19 pandemic has negatively impacted, and may continue to negatively impact our ability to develop our product candidates.

The impact of the ongoing COVID-19 pandemic has resulted in, and will likely continue to result in, significant disruptions to the global economy, as well as businesses and capital markets around the world. Efforts to contain the spread of COVID-19 have intensified at times to manage surges in the infection rate and deaths, and many countries have at times implemented severe travel restrictions, social distancing, and delays or cancellations of elective surgeries at different times. Notwithstanding the introduction of effective vaccines, COVID-19 is expected to continue affecting our ability and the ability of our employees, contractors, suppliers, and other partners to conduct normal business activities from time to time, including due to shutdowns that may be requested or mandated by governmental authorities.

The continued spread of COVID-19 globally has adversely impacted and may continue to impact our operations. We have initiated several clinical trials and plan in the near future to initiate an additional clinical trial for istaroxime in the EU and other worldwide locations impacted by the COVID-19 outbreak. Our ongoing clinical trials have suffered delays and interruptions and our decision to cease enrollment in the AEROSURF clinical trial was partially due to such delays and escalating expenses. Our ongoing efforts to conduct these trials could be materially delayed in the future by governmental restrictions and enrollment difficulties as hospitals reduce and divert staffing, divert resources to patients suffering from the infectious disease and limit hospital access for nonpatients.

Similarly, there is a risk that clinical supplies of our product candidates may be significantly delayed or may become unavailable as a result of COVID-19 and the resulting impact on our suppliers' labor forces and operations, including as a result of governmental restrictions on business operations and the movement of people and goods in an effort to curtail the spread of the virus. There can be no assurance that we would be able to timely implement any mitigation plans. Disruptions in our supply chain, whether as a result of restricted travel, quarantine requirements or otherwise, could negatively impact clinical supplies of our product candidates, which could materially adversely impact our clinical trial and development timelines.

The continued spread of COVID-19, including potential new variants, has also led to periodic disruption and volatility in the global capital markets, which could increase our cost of capital and adversely affect our ability to access the capital markets in the future. It is possible that the continued spread of COVID-19 could cause an economic slowdown or recession or cause other unpredictable events, each of which could adversely affect our business, results of operations or financial condition.

The extent to which COVID-19 impacts our financial results going forward will depend on future developments, which are highly uncertain and cannot be predicted, including new information which may emerge concerning the severity of the COVID-19 outbreak, the rise of variants, which may be more contagious and potentially more lethal, and the actions recommended to contain the outbreak or treat its impact, among others. Moreover, the COVID-19 outbreak has had indeterminable adverse effects on general commercial activity and the world economy, and our business and results of operations could be adversely affected to the extent that COVID-19 or any other pandemic harms the global economy generally.

Use of our product candidates could be associated with side effects, adverse events or other properties or safety risks, which could delay or preclude approval, cause us to suspend or discontinue clinical trials, abandon a product candidate, limit the commercial profile of an approved label or result in other significant negative consequences that could severely harm our business, prospects, operating results and financial condition.

As is the case with pharmaceuticals generally, there may be adverse events in patients treated with our product candidates. Results of our clinical trials could reveal a high and unacceptable severity and prevalence of side effects or unexpected characteristics. Undesirable side effects caused by our product candidates could cause us or regulatory authorities to interrupt, delay or halt clinical trials and could result in a more restrictive label or the delay or denial of regulatory approval by the FDA or comparable foreign regulatory authorities. Adverse events could affect patient recruitment or the ability of enrolled patients to complete the trial or result in potential product liability claims. Any of these occurrences may harm our business, financial condition and prospects significantly.

Moreover, if our product candidates are associated with undesirable side effects in clinical trials or have characteristics that are unexpected, we may elect to abandon their development or limit their development to more narrow uses or subpopulations in which the undesirable side effects or other characteristics are less prevalent, less severe or more acceptable from a risk-benefit perspective, which may limit the commercial expectations for the product candidate if approved. We may also be required to modify our study plans based on findings in our ongoing clinical trials. Many compounds that initially show promise in early-stage testing have later been found to cause side effects that prevented further development of the compound. In addition, regulatory authorities may draw different conclusions or require additional testing to confirm these determinations.

It is possible that as we test our product candidates in larger, longer and more extensive clinical trials, or as the use of these product candidates becomes more widespread if they receive regulatory approval, illnesses, injuries, discomforts and other adverse events that were observed in earlier trials, as well as conditions that did not occur or went undetected in previous trials, will be reported by subjects. If such side effects become known later in development or upon approval, if any, such findings may harm our business, financial condition and prospects significantly.

In addition, if one or more of our product candidates receives marketing approval, and we or others later identify undesirable side effects caused by such products, a number of potentially significant negative consequences could result, including:

- regulatory authorities may withdraw, suspend or limit approvals of such product;
- we may be required to recall a product or change the way such product is administered to patients;
- regulatory authorities may require additional warnings on the label, such as a "black box" warning or a contraindication;
- we may be required to implement a Risk Evaluation and Mitigation Strategy, or REMS, or create a medication guide outlining the risks of such side effects for distribution to patients;
- we may be required to change the way a product is distributed or administered, conduct additional clinical trials or change the labeling of a product or be required to conduct additional post-marketing studies or surveillance;
- we could be sued and held liable for harm caused to patients;
- sales of the product may decrease significantly, or the product could become less competitive; and
- our reputation may suffer.

Any of these events could prevent us from achieving or maintaining market acceptance of the particular product candidate, if approved, and could significantly harm our business, results of operations and prospects.

Our product candidates are subject to extensive regulation and compliance, which is costly and time consuming, and such regulation may cause unanticipated delays or prevent the receipt of the required approvals to commercialize our product candidates.

The clinical development, manufacturing, labeling, storage, record-keeping, advertising, promotion, import, export, marketing and distribution of our product candidates are subject to extensive regulation by the FDA in the U.S. and by comparable foreign regulatory authorities in foreign markets. In the U.S., the process of obtaining regulatory approval is expensive, often takes many years following the commencement of clinical trials and can vary substantially based upon the type, complexity and novelty of the product candidates involved, as well as the target indications and patient population. Approval policies or regulations may change, and the FDA has substantial discretion in the drug approval process, including the ability to delay, limit or deny approval of a product candidate for many reasons. Despite the time and expense invested in clinical development of product candidates, regulatory approval is never guaranteed. We are not permitted to market any of our product candidates in the U.S. until we receive approval of a New Drug Application, or NDA, from the FDA.

Prior to obtaining approval to commercialize a product candidate in the U.S. or abroad, we must demonstrate with substantial evidence from adequate and well-controlled clinical trials, and to the satisfaction of the FDA or comparable foreign regulatory authorities, that such product candidates are safe and effective for their intended uses.

Even if we believe the nonclinical or clinical data for our product candidates are promising, such data may not be sufficient to support approval by the FDA and comparable foreign regulatory authorities. The FDA or comparable foreign regulatory authorities, as the case may be, may also require us to conduct additional preclinical studies or clinical trials for our product candidates either prior to or post-approval, or may object to elements of our clinical development program.

The FDA or comparable foreign regulatory authorities can delay, limit or deny approval of a product candidate for many reasons, including:

- such authorities may disagree with the design or implementation of our clinical trials;
- negative or ambiguous results from our clinical trials or results may not meet the level of statistical significance required by the FDA or comparable foreign regulatory agencies for approval;
- such authorities may disagree with our interpretation of data from preclinical studies or clinical trials;
- such authorities may not agree that the data collected from clinical trials of our product candidates are acceptable or sufficient to support approval;
- serious and unexpected adverse events may be experienced by participants in our clinical trials or by individuals using drugs similar to our product candidates;
- the population studied in the clinical trial may not be sufficiently broad or representative to assure safety in the full population for which we seek approval;
- such authorities may not accept clinical data from trials which are conducted at clinical facilities or in countries where the standard of care or patient characteristics are potentially different from that of the U.S.;
- we may be unable to demonstrate that a product candidate's clinical and other benefits outweigh its safety risks or the safety data base may not be large enough;
- such authorities may not accept the submission of an NDA or other submission to obtain regulatory approval in the U.S. or elsewhere, and such authorities may impose requirements for additional preclinical studies or clinical trials;
- such authorities may disagree regarding the formulation, labeling and/or the specifications of our product candidates;
- approval may be granted only for indications that are significantly more limited than what we apply for and/or with other significant restrictions on distribution and use;
- such authorities may find deficiencies in the manufacturing processes or facilities of our third-party manufacturers with which we contract for clinical and, if approved, commercial supplies; or the approval policies;
- regulations of such authorities may significantly change in a manner rendering our or any of our potential future collaborators' clinical data insufficient for approval; or
- such authorities may not accept a submission due to, among other reasons, the content or formatting of the submission.

We may conduct clinical development in the U.S., Canada, the EU, Eastern Europe, Latin America, and Asia Pacific regions and sell our products in the U.S. and potentially in other major markets. To accomplish this objective, we must obtain and maintain regulatory approvals and comply with regulatory requirements in each jurisdiction. To avoid the significant expense and lengthy time required to complete multiple regional clinical development programs, we expect to meet with relevant regulatory authorities. While we would prefer to design a single, global clinical development program that would satisfy the regulators in all of our target markets, there can be no assurance that our efforts will be successful. If we are unable to reach agreement with the various regulatory authorities, we may not be able to pursue regulatory approval of our products in all of our selected markets.

With respect to foreign markets, approval procedures vary among countries and, in addition to the foregoing risks, may involve additional product testing, administrative review periods and agreements with pricing authorities. In addition, events raising questions about the safety of certain marketed pharmaceuticals may result in increased cautiousness by the FDA and comparable foreign regulatory authorities in reviewing new drugs based on safety, efficacy or other regulatory considerations and may result in significant delays in obtaining regulatory approvals. Any delay in obtaining, or inability to obtain, applicable regulatory approvals would prevent us or any of our potential future collaborators from commercializing our product candidates. In addition, delays associated with COVID-19 may impact local regulatory reviews occurring in a timely manner and result in delays for trial and site initiations.

Of the large number of drugs in development, only a small percentage successfully complete the FDA or foreign regulatory approval processes and are commercialized. The lengthy approval process as well as the unpredictability of future clinical trial results may result in our failing to obtain regulatory approval to market our product candidates, which would significantly harm our business, financial condition, results of operations and prospects.

If our competitors develop and receive FDA approval for treatments or vaccines for COVID-19, our commercial opportunity with respect to our development of KL4 surfactant for the treatment of lung injury and ARDS caused by COVID-19 may be reduced or eliminated.

There are numerous companies working on therapies to treat COVID-19 and/or vaccines to prevent or treat COVID-19. Multiple vaccines have received full FDA approval or emergency use authorization.

Furthermore, the FDA has authorized, and many companies are developing, therapeutics to treat COVID-19. The FDA requires us to conduct clinical trials for the approval of KL4 surfactant as a therapy for COVID-19-related lung injury and ARDS and enrollment in such trials may be impacted given the commercial availability of approved or authorized vaccines and/or therapies. The success or failure of other vaccines and/or therapies, or perceived success or failure, may adversely impact our ability to obtain any future funding for our KL4 surfactant development efforts or for us to ultimately commercialize any product candidate, if authorized or approved. In addition, we may not be able to compete effectively if our product candidate does not satisfy government procurement requirements with respect to biodefense products.

If competing therapies are approved, such approval could have a material adverse impact on our ability to commercialize KL4 surfactant as a therapy for COVID-19-related lung injury and ARDS. The speed at which all parties are acting to create and test many treatments and vaccines for COVID-19 is unusual and evolving or changing plans or priorities within the FDA and other branches of the U.S. government involved in the fight against the pandemic, including changes based on new knowledge of COVID-19, new COVID-19 variants and how the disease affects the human body, may significantly affect the regulatory timeline for KL4 surfactant. In addition, there are numerous clinical trial programs in progress for COVID-19 therapies which are all competing for largely the same patient population for enrollment. This problem is exacerbated by changing rates of infection and spread. Many of our competitors and potential competitors have substantially greater scientific, research, and product development capabilities, as well as greater financial, marketing, sales and human resources capabilities than we do. In addition, many specialized biotechnology firms have formed collaborations with large, established companies to support the research, development and commercialization of products that may be competitive with ours.

Because we have multiple product candidates in our clinical pipeline, we may expend our limited resources to pursue a particular product candidate and fail to capitalize on other product candidates or indications that may be more profitable or for which there is a greater likelihood of success.

Because we have limited financial and managerial resources, we may focus on specific product candidates, indications and development programs at any time. We also may plan to conduct several clinical trials for multiple product candidates in parallel over the next several years, which may make our decision as to the product candidates on which we will focus more difficult. As a result, we may forgo or delay pursuit of opportunities with other product candidates that could have had greater commercial potential. Our resource allocation decisions may cause us to fail to capitalize on viable commercial products or profitable market opportunities. Our spending on current and future research and development programs and product candidates for specific indications may not yield any commercially viable products. If we do not accurately evaluate the commercial potential or target market for a particular product candidate, we may relinquish valuable rights to that product candidate through future collaborations, license agreements and other similar arrangements in cases in which it would have been more advantageous for us to retain sole development and commercialization rights to such product candidate. For example, following a decision by our licensee in Asia to terminate a funding agreement for AEROSURF clinical development in the EU, we ceased our development activities for AEROSURF. To support the further development of AEROSURF, we are pursuing one or more licensing agreements. This decision was driven by our desire to focus on acute cardiovascular and other KL4 surfactant programs, primarily treatment of lung injury in patients with COVID-19.

Additionally, we may pursue additional in-licenses or acquisitions of development-stage assets or programs, which entails additional risk to us. Identifying, selecting and acquiring promising product candidates requires substantial technical, financial and human resources expertise. Efforts to do so may not result in the actual acquisition or license of a particular product candidate, potentially resulting in a diversion of our management's time and the expenditure of our resources with no resulting benefit. If we are unable to identify programs that ultimately result in approved products, we may spend material amounts of our capital, management and other resources evaluating, acquiring and developing products that ultimately do not provide a return on our investment.

Even though some of our product candidates have Fast Track designation, the FDA may not approve them at all or any sooner than other product candidates that do not have Fast Track designation.

We have received Fast Track designation from the FDA for istaroxime for the treatment of acute heart failure, or AHF. Fast Track designation does not ensure that we will receive marketing approval or that approval will be granted within any particular timeframe. We may not experience a faster development, regulatory review or approval process with Fast Track designation compared to conventional FDA procedures. Additionally, the FDA may withdraw Fast Track designation, for reasons such as it comes to believe a drug candidate no longer adequately addresses an unmet medical need. Fast Track designation alone does not guarantee qualification for the FDA's priority review procedures. If we seek Fast Track designation for other product candidates, we may not receive such a designation from the FDA.

Although we may pursue expedited regulatory programs for a product candidate or an indication, it may not qualify for expedited development or, if it does qualify for expedited development, it may not actually lead to a faster development or regulatory review or approval process.

Although we have received Fast Track designation for certain of our product candidates, we believe there may be an opportunity to expedite the development of other product candidates or indications through one or more of the FDA's expedited programs, such as Fast Track, Breakthrough Therapy or priority review, we cannot be assured that any of our product candidates or indications will qualify for such programs.

For example, a drug may be eligible for designation as a Breakthrough Therapy if the drug is intended, alone or in combination with one or more other drugs, to treat a serious or life-threatening condition and preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints. Although Breakthrough Therapy designation or access to any other expedited program may expedite the development or approval process, it does not change the standards for approval. If we apply for Breakthrough Therapy designation or any other expedited program for our product candidates, the FDA may determine that our proposed target indication or other aspects of our clinical development plans do not qualify for such expedited program. Even if we are successful in obtaining a Breakthrough Therapy designation or access to any other expedited program, we may not experience faster development timelines or achieve faster review or approval compared to conventional FDA procedures. Access to an expedited program may also be withdrawn by the FDA if it believes that the designation is no longer supported by data from our clinical development program. Additionally, qualification for any expedited program does not ensure that we will ultimately obtain regulatory approval for such product candidate.

In addition, we believe that istaroxime may fulfill an unmet medical need in early cardiogenic shock based on the profile observed in prior phase 2 clinical studies in AHF, in which istaroxime increased systolic blood pressure, or SBP, suggesting that istaroxime could potentially contribute to the clinical improvement of select patients in cardiogenic shock due to heart failure. If our ongoing clinical study is successful, we believe there may be an opportunity to explore an expedited regulatory pathway and review of istaroxime for the treatment of early cardiogenic shock.

We may not be able to obtain or maintain Orphan Drug exclusivity for our product candidates.

Regulatory authorities in some jurisdictions, including the U.S. and Europe, may designate drugs for relatively small patient populations as Orphan Drugs. In the U.S., Orphan Drug designation entitles a party to financial incentives such as tax advantages and user-fee waivers. In addition, if a product candidate that has Orphan Drug designation subsequently receives the first FDA approval for the disease for which it has such designation, the product is entitled to Orphan Drug exclusivity, which means that the FDA may not approve any other applications, including an NDA, to market the same drug for the same indication for seven years, except in limited circumstances, including if the FDA concludes that the later drug is clinically superior to the approved drug. A drug is clinically superior if it is safer, more effective, or makes a major contribution to patient care. The FDA has granted Orphan Drug designation for our (i) KL4 surfactant (lucinactant) for the treatment of RDS in premature infants, (ii) our KL4 surfactant for the prevention and treatment of BPD in premature infants, (iii) our KL4 surfactant for the treatment of ARDS in adults, and (iv) our KL4 surfactant for the treatment of cystic fibrosis.

If we obtain Orphan Drug exclusivity, we may lose such exclusivity if the FDA or the European Commission, or EC, determines that the request for designation was materially defective or if we are unable to assure sufficient quantity of the drug to meet the needs of patients with the rare disease or condition. Moreover, Orphan Drug exclusivity may not effectively protect our product candidates from competition because different drugs can be approved for the same condition. Even after an Orphan Drug is approved, the FDA or comparable foreign regulatory authority can subsequently approve the same drug for the same condition if such regulatory authority concludes that the later drug is clinically superior if it is shown to be safer, more effective or makes a major contribution to patient care. Orphan drug designation neither shortens the development time or regulatory review time of a drug nor gives the drug any advantage in the regulatory review or approval process.

Interim, topline and preliminary data from our clinical trials that we announce or publish from time to time may change as more patient data become available and are subject to audit and verification procedures that could result in material changes in the final data.

From time to time, we may publicly disclose preliminary or topline or data from our clinical studies, which is based on a preliminary analysis of then-available data, and the results and related findings and conclusions are subject to change following a more comprehensive review of the data related to the particular study or trial. We also make assumptions, estimations, calculations and conclusions as part of our analyses of data, and we may not have received or had the opportunity to fully and carefully evaluate all data. As a result, the topline results that we report may differ from future results of the same studies, or different conclusions or considerations may qualify such results once additional data have been received and fully evaluated. Topline data also remain subject to audit and verification procedures that may result in the final data being materially different from the preliminary data we previously published. As a result, topline data should be viewed with caution until the final data are available. From time to time, we may also disclose interim data from our clinical studies. Interim data from clinical trials that we may complete are subject to the risk that one or more of the clinical outcomes may materially change as patient enrollment continues and more patient data become available. Adverse differences between preliminary or interim data and final data could significantly harm our business prospects.

Even if we receive regulatory approval for any product candidates, we will be subject to ongoing regulatory obligations and continued regulatory review, which may result in significant additional expense. Additionally, our product candidates, if approved, could be subject to labeling and other restrictions on marketing or withdrawal from the market, and we may be subject to penalties if we fail to comply with regulatory requirements or if we experience unanticipated problems with our product candidates, when and if any of them are approved.

Following potential approval of any our product candidates, the FDA may impose significant restrictions on a product's indicated uses or other aspects of the directions for use or marketing or impose ongoing requirements for potentially costly and time-consuming post-approval studies, post-market surveillance or clinical trials to monitor the safety and efficacy of the product. The FDA may also require a REMS as a condition of approval of our product candidates, which could include requirements for a medication guide, physician communication plans or additional elements to ensure safe use, such as restricted distribution methods, patient registries and other risk minimization tools. In addition, if the FDA or a comparable foreign regulatory authority approves our product candidates, the manufacturing processes, labeling, packaging, distribution, adverse event reporting, storage, advertising, promotion, import, export and recordkeeping for our products will be subject to extensive and ongoing regulatory requirements. These requirements include submissions of safety and other post-marketing information and reports, registration, as well as continued compliance with cGMPs and GCP requirements for any clinical trials that we conduct post-approval. Later discovery of previously unknown problems with our products, including adverse events of unanticipated severity or frequency, or with our third-party manufacturers or manufacturing processes, or failure to comply with regulatory requirements, may result in, among other things:

- restrictions on the marketing or manufacturing of our products, withdrawal of the product from the market or voluntary or mandatory product recalls;
- restrictions on product distribution or use, or requirements to conduct post-marketing studies or clinical trials;
- fines, restitutions, disgorgement of profits or revenues, warning letters, untitled letters or holds on clinical trials;
- refusal by the FDA to approve pending applications or supplements to approved applications filed by us or suspension or revocation of approvals;
- product seizure or detention, or refusal to permit the import or export of our products; and
- injunctions or the imposition of civil or criminal penalties.

The occurrence of any event or penalty described above may inhibit our ability to commercialize our product candidates and generate revenue and could require us to expend significant time and resources in response and could generate negative publicity.

In addition, if any of our product candidates is approved, our product labeling, advertising and promotion will be subject to regulatory requirements and continuing regulatory review. The FDA strictly regulates the promotional claims that may be made about drug products. In particular, a product may not be promoted for uses that are not approved by the FDA as reflected in the product's approved labeling. If we receive marketing approval for a product candidate, physicians may nevertheless prescribe it to their patients in a manner that is inconsistent with the approved label. If we are found to have promoted such off-label uses, we may become subject to significant liability.

The FDA's and other regulatory authorities' policies may change and additional government regulations may be enacted that could prevent, limit or delay regulatory approval of our product candidates. If we are slow or unable to adapt to changes in existing requirements or the adoption of new requirements or policies, or if we are not able to maintain regulatory compliance, we may lose any marketing approval that we may have obtained and we may not achieve or sustain profitability.

If we fail to obtain and maintain regulatory approval in foreign jurisdictions, our market opportunities will be limited.

In order to market our product candidates in the EU or other foreign jurisdictions, we must obtain and maintain separate regulatory approvals and comply with numerous and varying regulatory requirements. The approval procedure varies from country to country and can involve additional testing. The time required to obtain approval abroad may be longer than the time required to obtain FDA clearance or approval. Foreign regulatory approval processes include many of the risks associated with obtaining FDA clearance or approval and we may not obtain foreign regulatory approvals on a timely basis, if at all. FDA clearance or approval does not ensure approval by regulatory authorities in other countries, and approval by one foreign regulatory authority does not ensure approval by regulatory authorities in other foreign countries. However, the failure to obtain clearance or approval in one jurisdiction may have a negative impact on our ability to obtain clearance or approval elsewhere. If we do not obtain or maintain necessary approvals to commercialize our product candidates in markets outside the U.S., it would negatively affect our overall market penetration.

If the FDA or other applicable regulatory authorities approve generic products with claims that compete with our product candidates, it could reduce our sales of our product candidates if approved.

In the U.S., after an NDA is approved, the product covered thereby becomes a "listed drug" which can, in turn, be cited by potential competitors in support of approval of an abbreviated NDA, or ANDA. The Federal Food, Drug, and Cosmetic Act, or the FDC Act, FDA regulations and other applicable regulations and policies provide incentives to manufacturers to create modified, non-infringing versions of a drug to facilitate the approval of an ANDA or other application for generic substitutes. These manufacturers might only be required to conduct a relatively inexpensive study to show that their product has the same active ingredients, dosage form, strength, route of administration, and conditions of use, or product labeling, as our product candidates and that the generic product is absorbed in the body at the same rate and to the same extent as, or is bioequivalent to, our product candidates. These generic equivalents would be significantly less costly than ours to bring to market and companies that produce generic equivalents are generally able to offer their products at lower prices. Thus, after the introduction of a generic competitor, a significant percentage of the sales of any branded product are typically lost to the generic product. Accordingly, competition from generic equivalents to our product candidates would substantially limit our ability to generate revenues and therefore to obtain a return on the investments we have made in our product candidates.

Even if we receive regulatory approval for any of our product candidates, we may not be able to successfully commercialize the product and the revenue that we generate from its sales, if any, may be limited.

If approved for marketing, the commercial success of our product candidates will depend upon the acceptance of each product by the medical community, including physicians, patients and health care payors. The degree of market acceptance for any of our product candidates will depend on a number of factors, including:

- demonstration of clinical safety and efficacy;
- efficacy of our product candidates compared to competing products;
- relative convenience, dosing burden and ease of administration;
- the prevalence and severity of any adverse effects;
- the willingness of physicians to prescribe our product candidates, and the target patient population to try new therapies;

- our ability to obtain and maintain sufficient third-party coverage or reimbursement from government health care programs, including Medicare and Medicaid, global government payors, private health insurers and other third-party payors or to receive the necessary pricing approvals from government bodies regulating the pricing and usage of therapeutics;
- the willingness of patients to pay out-of-pocket in the absence of third-party coverage or reimbursement or government pricing approvals;
- government health care payor imposed mandatory pricing discounting and reductions;
- delays in achieving hospital formulary acceptance or limitations of use that are more restrictive than the approved label;
- the introduction of any new products that may in the future become available targeting indications for which our product candidates may be approved;
- new procedures or therapies that may reduce the incidences of any of the indications in which our product candidates may show utility;
- pricing and cost-effectiveness;
- the inclusion or omission of our product candidates in applicable therapeutic guidelines;
- the effectiveness of our own or any future collaborators' sales and marketing strategies; and
- limitations or warnings contained in approved labeling from regulatory authorities.

If any of our product candidates are approved, but do not achieve an adequate level of acceptance by physicians, health care payors, and patients, we may not generate sufficient revenue and we may not be able to achieve or sustain profitability. Our efforts to educate the medical community and third-party payors on the benefits of our product candidates may require significant resources and may never be successful.

In addition, even if we obtain regulatory approvals, the timing or scope of any approvals may prohibit or reduce our ability to commercialize our product candidates successfully. For example, if the approval process takes too long, we may miss market opportunities and give other companies the ability to develop competing products or establish market dominance. Any regulatory approval we ultimately obtain may be limited or subject to restrictions or post-approval commitments that render our product candidates not commercially viable. For example, regulatory authorities may approve any of our product candidates for fewer or more limited indications than we request, may grant approval contingent on the performance of costly post-marketing clinical trials, or may approve any of our product candidates with a label that does not include the labeling claims necessary or desirable for the successful commercialization for that indication. Further, the FDA or comparable foreign regulatory authorities may place conditions on approvals or require risk management plans or a REMS to assure the safe use of the drug. Any of these limitations on approval or marketing could restrict the commercial promotion, distribution, prescription or dispensing of our product candidates. Moreover, product approvals may be withdrawn for non-compliance with regulatory standards or if problems occur following the initial marketing of the product. Any of the foregoing scenarios could materially harm the commercial success of our product candidates.

The FDA and other regulatory agencies actively enforce the laws and regulations prohibiting the promotion of off- label uses. If we are found or alleged to have improperly promoted any of our products, if approved, for off-label uses, we may become subject to significant liability.

The FDA and other regulatory agencies strictly regulate the promotional claims that may be made about prescription products, as our product candidates would be, if approved. In general, a product may not be promoted for uses that are not approved by the FDA or in ways that may not be consistent with the product's approved labeling. If we are found to have promoted such off-label uses, we may become subject to significant liability. The federal government has levied large civil and criminal fines against companies for alleged improper promotion and has enjoined several companies from engaging in off-label promotion. The FDA and other regulatory agencies have also requested that companies enter into consent decrees or permanent injunctions under which specified promotional conduct is changed or curtailed. If we cannot successfully manage the promotion of our product candidates, if approved, we could become subject to significant liability, which would materially adversely affect our business and financial condition.

We currently have no sales and marketing organization. If we are unable to establish satisfactory sales and marketing capabilities or secure a sales and marketing partner, we may not successfully commercialize any of our product candidates.

We may not be able to enter into collaboration agreements on terms acceptable to us or at all. In addition, even if we enter into such relationships, we may have limited or no control over the sales, marketing and distribution activities of these third parties. Our future revenues may depend heavily on the success of the efforts of these third parties. If we elect to establish a sales and marketing infrastructure, we may not realize a positive return on this investment. In addition, we will have to compete with established and well-funded pharmaceutical and biotechnology companies to recruit, hire, train and retain sales and marketing personnel. Factors that may inhibit our efforts to commercialize our product candidates without strategic partners or licensees include:

- the inability of sales personnel to obtain access to or educate and appropriately persuade adequate numbers of physicians to prescribe any of our product candidates;
- inability to obtain a competitive share of voice and frequency of meeting with physicians against multiple, larger competitors;
- unforeseen costs and expenses associated with creating an independent sales and marketing organization; and
- inability to control or influence partner sales and marketing personnel or their prioritization of promotion of our product candidates.

The successful commercialization of our product candidates, if approved, will depend in part on the extent to which governmental authorities and health insurers establish coverage, adequate reimbursement levels and favorable pricing policies. Failure to obtain or maintain coverage and adequate reimbursement for our product candidates could limit our ability to market those product candidates and decrease our ability to generate revenue.

The availability of coverage and the adequacy of reimbursement by governmental healthcare programs such as Medicare and Medicaid, private health insurers and other third-party payors are essential for most patients to be able to afford prescription medications such as our product candidates, if approved. Our ability to achieve coverage and acceptable levels of reimbursement for our products by third-party payors will have an effect on our ability to successfully commercialize our products. Even if we obtain coverage for a given product by a third-party payor, the resulting reimbursement payment rates may not be adequate or may require co-payments that patients find unacceptably high. We cannot be sure that coverage and reimbursement in the U.S., the EU or elsewhere will be available for any product that we may develop, and any reimbursement that may become available may be decreased or eliminated in the future.

Third-party payors increasingly are challenging prices charged for pharmaceutical products and services, and many third-party payors may refuse to provide coverage and reimbursement for particular drugs when an equivalent generic drug or a less expensive therapy is available. It is possible that a third-party payor may consider our products as substitutable and only offer to reimburse patients for the less expensive product. Even if we are successful in demonstrating improved efficacy or improved convenience of administration with our products, pricing of existing drugs may limit the amount we will be able to charge for our products. These payors may deny or revoke the reimbursement status of a given product or establish prices for new or existing marketed products at levels that are too low to enable us to realize an appropriate return on our investment in product development. If reimbursement is not available or is available only at limited levels, we may not be able to successfully commercialize our products and may not be able to obtain a satisfactory financial return on products that we may develop.

There is significant uncertainty related to third-party payor coverage and reimbursement of newly approved products. In the U.S., third-party payors, including private and governmental payors, such as the Medicare and Medicaid programs, play an important role in determining the extent to which new drugs will be covered. Some third-party payors may require pre-approval of coverage for new or innovative devices or drug therapies before they will reimburse healthcare providers who use such therapies. It is difficult to predict at this time what third-party payors will decide with respect to the coverage and reimbursement for our products.

Obtaining and maintaining reimbursement status is time consuming, costly and uncertain. The Medicare and Medicaid programs increasingly are used as models for how private payors and other governmental payors develop their coverage and reimbursement policies for drugs. However, no uniform policy for coverage and reimbursement for products exists among third-party payors in the U.S. Therefore, coverage and reimbursement for products can differ significantly from payor to payor. As a result, the coverage determination process is often a time consuming and costly process that will require us to provide scientific and clinical support for the use of our products to each payor separately, with no assurance that coverage and adequate reimbursement will be applied consistently or obtained in the first instance. Furthermore, rules and regulations regarding reimbursement change frequently, in some cases at short notice, and we believe that changes in these rules and regulations are likely.

Outside the U.S., international operations are generally subject to extensive governmental price controls and other market regulations, and we believe the increasing emphasis on cost-containment initiatives in Europe and other countries has and will continue to put pressure on the pricing and usage of our products. In many countries, the prices of medical products are subject to varying price control mechanisms as part of national health systems. Additional foreign price controls, discounts or other changes in pricing regulation could restrict the amount that we are able to charge for our products. Accordingly, in markets outside the U.S., the reimbursement for our products may be reduced and experience continual mandatory price reductions compared with the U.S. and may be insufficient to generate commercially reasonable revenue and profits.

Moreover, increasing efforts by governmental and third-party payors in the U.S. and abroad to cap or reduce healthcare costs may cause such organizations to limit both coverage and the level of reimbursement for newly approved products and, as a result, they may not cover or provide adequate payment for our products. We expect to experience pricing pressures in connection with the sale of any of our products due to the trend toward managed healthcare, the increasing influence of health maintenance organizations and additional legislative changes. The downward pressure on healthcare costs in general, particularly prescription drugs and surgical procedures and other treatments, has become very intense. As a result, increasingly high barriers are being erected to the entry of new products.

Risks Related to Our Reliance on Third Parties

We rely on third parties, primarily outside of the U.S., to conduct many of our preclinical studies and clinical trials. Any failure by a third party to conduct the clinical trials according to GCPs and other requirements and in a timely manner may delay or prevent our ability to seek or obtain regulatory approval for or commercialize our product candidates.

We are dependent on third parties to conduct our clinical trials and preclinical studies and preclinical studies for our other development programs. Specifically, we have used and relied on, and intend to continue to use and rely on, medical institutions, clinical investigators, CROs and consultants to conduct our clinical trials in accordance with our clinical protocols and regulatory requirements. These CROs, investigators and other third parties play a significant role in the conduct and timing of these trials and subsequent collection and analysis of data. While we have agreements governing the activities of our third-party contractors, we have limited influence over their actual performance. Nevertheless, we are responsible for ensuring that each of our clinical trials is conducted in accordance with the applicable protocol and legal, regulatory and scientific standards, and our reliance on the CROs and other third parties does not relieve us of our regulatory responsibilities. We and any third-party that we rely upon are required to comply with GCP requirements, which are regulations and guidelines enforced by the FDA and comparable foreign regulatory authorities for all of our product candidates in clinical development. Regulatory authorities enforce these GCPs through periodic inspections of trial sponsors, principal investigators and trial sites. If we or any third-party that we rely on or trial sites fail to comply with applicable GCPs or to provide adequate data with respect to such trials, the clinical data generated in our clinical trials may be deemed unreliable, and the FDA or comparable foreign regulatory authorities may require us to perform additional clinical trials before approving our marketing applications. In addition, our clinical trials must be conducted with product produced under cGMP and/or Quality System Regulation, or QSR requirements. Our failure to comply with these regulations may require us to repeat clinical trials, which would delay the regulatory approval process.

There is no guarantee that any such CROs, investigators or other third parties will devote adequate time and resources to such trials or perform as contractually required. If any of these third parties fail to meet expected deadlines, adhere to our clinical protocols or meet regulatory requirements, or otherwise performs in a substandard manner, our clinical trials may be extended, delayed or terminated. In addition, many of the third parties with whom we contract may also have relationships with other commercial entities, including our competitors, for whom they may also be conducting clinical trials or other drug development activities that could harm our competitive position. In addition, principal investigators for our clinical trials may serve as scientific advisors or consultants to us from time to time and may receive cash or equity compensation in connection with such services. If these relationships and any related compensation result in perceived or actual conflicts of interest, or the FDA concludes that the financial relationship may have affected the interpretation of the study, the integrity of the data generated at the applicable clinical trial site may be questioned and the utility of the clinical trial itself may be jeopardized, which could result in the delay or rejection by the FDA of any NDA we submit. Any such delay or rejection could prevent us from commercializing our product candidates.

If any of our relationships with these third parties terminate, we may not be able to enter into arrangements with alternative third parties or do so on commercially reasonable terms. Switching or adding additional CROs, investigators and other third parties involves additional costs and requires management time and focus. In addition, there is a natural transition period when a new CRO commences work. As a result, delays occur, which can materially impact our ability to meet our desired clinical development timelines. Though we carefully manage our relationships with our CROs, investigators and other third parties, there can be no assurance that we will not encounter challenges or delays in the future or that these delays or challenges will not have a material adverse impact on our business, financial condition and prospects.

We currently do not have a back-up facility for our CMO for our drug product candidates, or our suppliers of APIs. If the parties we depend on for supplying our APIs and manufacturing our drug product candidates do not supply these products in a timely manner, it may delay or impair our ability to execute our development plans for our current and potential pipeline products. Such delays could adversely impact our operations and financial condition.

In most cases, we are dependent upon a single supplier to provide all of our requirements for each of our APIs. We rely on a single CMO, located in China, to manufacture each of our drug product candidates that meets appropriate content, quality and stability standards for use in preclinical programs and clinical trials. In most cases, we submit purchase orders to our CMO and API suppliers as needed and do not have contractual commitments to manufacture for us in the future. If we do not maintain these manufacturing and service relationships that are important to us and are not able to identify replacement suppliers, vendors and laboratories, our ability to obtain regulatory approval for our product candidates could be impaired or delayed and our costs could substantially increase.

We may be unable to identify additional manufacturers with whom we might establish appropriate arrangements on acceptable terms, if at all, because the number of potential CMOs is limited. Even if we are able to find replacement manufacturers, suppliers, vendors and service providers when needed, we may not be able to enter into agreements with them on terms and conditions favorable to us or there could be a substantial delay before such manufacturer, vendor or supplier, or a related new facility is properly qualified and registered with the FDA or other foreign regulatory authorities. A new manufacturer currently not qualified with the FDA would have to be educated in, or develop substantially equivalent processes for, production of our approved products after receipt of FDA approval. To qualify and receive regulatory approval for a new manufacturer could take as long as two years. The process of changing a supplier could have an adverse impact on our current clinical development programs if supplies of drug substances or materials on hand are insufficient to satisfy demand. Such delays could have a material adverse effect on our development activities and our business.

We plan to rely on third parties, some of which are located outside the U.S., to manufacture our drug product candidates, which exposes us to risks that may affect our ability to maintain supplies of our clinical materials, and subject us to uncertainty associated with the international political climate, and could potentially delay our research and development activities, as well as eventual regulatory approval and commercialization of our drug product candidates.

Our manufacturing strategy involves manufacturing our drug product candidates using a CMO. We do not own or operate manufacturing facilities and have no plans to build our own clinical or commercial scale manufacturing capabilities. We rely, and expect to continue to rely, on third parties for the manufacture of our drug product candidates and related raw materials for clinical and preclinical development, as well as for commercial manufacture if any of our product candidates receive marketing approval. The facilities used by third-party manufacturers to manufacture our product candidates must be approved by the FDA pursuant to inspections that will be conducted after we submit an NDA to the FDA. We do not control the manufacturing process of, and are completely dependent on, third-party manufacturers for compliance with cGMP requirements for manufacture of drug products and QSR requirements for the manufacture of medical devices and other government regulations and corresponding international standards. If these third-party manufacturers cannot successfully manufacture material that conforms to our specifications and the strict regulatory requirements of the FDA or others, including requirements related to the manufacturing of high potency compounds, they will not be able to secure and/or maintain regulatory approval for their manufacturing facilities.

Istaroxime and rostafuroxin are currently manufactured by an affiliate of Lee's (HK) in Hefei, China. We expect that Lee's (HK) will manufacture KL4 surfactant drug product candidate at an affiliate of Lee's (HK) in Hefei, China. The APIs for istaroxime and rostafuroxin are manufactured in China and the APIs for KL4 surfactant are manufactured in the U.S. If the FDA is unable to inspect the manufacturing site in China or if it is able to inspect the site but finds it deficient in any way, to secure marketing approval for our product candidates in the U.S., and potentially other markets, we may be required to designate a different manufacturer for each of our drug product candidates. A technology transfer of a manufacturing process from one CMO to another can be time consuming and expensive and there can be no assurance that such a transfer will be successful or that a new manufacturer will be able to manufacture our drug product candidates successfully. Moreover, a technology transfer from one country to another may be subject to changing international legal and regulatory requirements in a potential difficult political climate. In addition, we have limited control over the ability of third-party manufacturers to maintain adequate quality control, quality assurance and qualified personnel and the third-party manufacturers may fail to manufacture our product candidate according to our schedule or at all. If the FDA or a comparable foreign regulatory authority does not approve these facilities for the manufacture of our product candidates or if it withdraws any such approval in the future, we may need to find alternative manufacturing facilities, which would significantly impact our ability to develop, obtain regulatory approval for or market our product candidates, if approved. Our failure, or the failure of our third-party manufacturers, to comply with applicable regulations could result in sanctions being imposed on us, including clinical holds, fines, injunctions, civil penalties, delays, suspension or withdrawal of approvals, seizures or recalls of product candidates or products, operating restrictions and criminal prosecutions, any of which could significantly and adversely affect supplies of our product candidates. In addition, any performance failure on the part of our existing or future manufacturers could delay clinical development or marketing approval, and any related remedial measures may be costly or time consuming to implement. We do not currently have arrangements in place for redundant supply or a second source for all required raw materials used in the manufacture of our product candidates. If our current third-party manufacturer cannot perform as agreed, we may be required to replace such manufacturers and we may be unable to replace them on a timely basis or at all.

A third party's failure to execute on our manufacturing requirements, technology transfers of our manufacturing and our planned future reliance on CMOs exposes us, among other things, to the following risks:

- an inability to initiate or continue clinical trials of istaroxime or any future product candidates under development;
- subjecting third-party manufacturing facilities to additional inspections by regulatory authorities;
- we may implement a plan to execute a technology transfer of our manufacturing process to a CMO and, after investing significant time and resources, learn that the CMO we chose is unable to successfully complete the technology transfer and thereafter manufacture our product candidates in accordance with our plan;
- CMOs might be unable to manufacture our product candidates in the volume and to our specifications to meet our clinical and commercial needs, or we may have difficulty scheduling the production of drug product and devices in a timely manner to meet our timing requirements;
- if we desire to make our drug product candidates and/or devices available outside the U.S. for clinical or commercial purposes, our CMOs would become subject to, and may not be able to comply with, corresponding manufacturing and quality system regulations or standards of the various foreign regulators having jurisdiction over our activities abroad. Such failures (such as in-country quality testing) could result in not only a loss of approved supply to that country, but a total loss of a lot (or lots) of materials globally and could restrict our ability to execute our business strategies;
- we may have difficulty implementing changes or necessary modifications to our manufacturing processes that may be required by the FDA or foreign regulator or our CMO, if, for example, such changes would burden our CMO or otherwise disrupt operations, or our CMO could impose significant financial terms to implement any such change that could adversely affect our business. We may fail to adequately develop new manufacturing processes. Failure to achieve such required changes or modifications could delay or prevent our gaining regulatory approval for our product candidates or prevent us from continuing to market our approved products, which would have a material adverse effect on our business, financial condition and operations;
- we may fail to adequately scale manufacturing to achieve our objectives for cost of goods and profit margins;
- we may be subject to disputes arising with respect to the ownership of rights to any technology developed with third parties; and
- we may be subject to the misappropriation of our proprietary information, including our trade secrets and know-how.

Each of the foregoing risks and others could delay our development programs and, if approved, commercial manufacturing plans, limit our ability to maintain continuity of supply for our approved products, delay or impair the approval, if any, of our product candidates by the FDA, or result in higher costs or deprive us of potential product revenues.

In addition, our product candidates and any products that we may develop may compete with other product candidates and products for access to manufacturing facilities. There are a limited number of manufacturers that operate under cGMP regulations and that might be capable of manufacturing for us.

Our current and anticipated future dependence upon others for the manufacture of our product candidates or products may adversely affect our future profit margin and our ability to commercialize any products that receive marketing approval on a timely and competitive basis.

Our ability to manufacture our product candidates depends upon receiving adequate supplies and related services, which may be difficult or uneconomical to procure.

Supply chain or manufacturing interruptions could negatively impact our operations and financial performance. In connection with our drug product manufacturing activities, for certain of our product candidates, we own certain specialized manufacturing equipment installed at our CMO. However, we do not have fully redundant systems and equipment to respond promptly in the event of a significant loss at a CMO's manufacturing operations. Under certain conditions, we may be unable to produce our drug product candidates at the required volumes or to appropriate standards, if at all. The supply of any of our manufacturing materials may be interrupted because of supply shortages, poor vendor performance or other events outside our control, which may require us, among other things, to identify alternate vendors, which could involve a lengthy process, and result in increased expenses.

Risks Related to our Business and Operations

Our operating results may fluctuate significantly, which makes our future operating results difficult to predict and could cause our operating results to fall below expectations or any guidance we may provide.

Our quarterly and annual operating results may fluctuate significantly, which makes it difficult for us to predict our future operating results.

These fluctuations may occur due to a variety of factors, many of which are outside of our control, including, but not limited to:

- the timing and cost of, and level of investment in, research, development, including manufacturing development regulatory approval and commercialization activities relating to our product candidates, which may change from period to period;
- the timing and success or failure of preclinical studies or clinical trials for our product candidates or competing product candidates, or any other change in the competitive landscape of our industry, including consolidation among our competitors or partners;

- the level of investment funding we are able to achieve and apply to our development operations;
- the cost of manufacturing our product candidates, which may vary depending on the quantity of production and the terms of our agreements with third-party manufacturers;
- the timing and amount of the milestone or other payments we must make to the licensors and other third parties from whom we have in-licensed our acquired our product candidates;
- expenditures that we may incur to acquire, develop or commercialize additional product candidates and technologies;
- our allocation of resources and ability to raise additional capital;
- future changes in requirements to achieve regulatory approval;
- future accounting pronouncements or changes in our accounting policies.
- the capital markets stability and openness to investing;
- delays associated with COVID-19 which will impact the ability of our healthcare systems and trial sites to conduct trials to varied degrees and times;
- coverage and reimbursement policies with respect to our product candidates, if approved, and potential future drugs that compete with our products; and
- the level of demand for any approved products, which may vary significantly.

The cumulative effects of these factors could result in large fluctuations and unpredictability in our quarterly and annual operating results. As a result, comparing our operating results on a period-to-period basis may not be meaningful. Investors should not rely on our past results as an indication of our future performance.

This variability and unpredictability could also result in our failing to meet the expectations of industry or financial analysts or investors for any period. If our revenue or operating results fall below the expectations of analysts or investors or below any forecasts we may provide to the market, or if the forecasts we provide to the market are below the expectations of analysts or investors, the price of our common stock could decline substantially. Such a stock price decline could occur even when we have met any previously publicly stated revenue or earnings guidance we may provide.

We are continually evaluating our business strategy and may modify this strategy to respond to developments in our business and other factors, and any such modification, if not successful, could have a material adverse effect on our business, financial condition, and results of operations.

We plan to continually evaluate our business strategy and will modify our plans as necessary to achieve our objectives. In 2020, we modified our business strategy to preserve our limited capital and focus primarily on acute cardiovascular and KL4 surfactant for the treatment of lung injury in patients with COVID-19 and other similar indications. As part of our shift in priorities, our licensee in Asia is expected to continue the further development of AEROSURF for the treatment of RDS in China pursuant to the terms of our Asia License Agreement. For markets outside of Asia, including the U.S., we plan in the short term to seek one or more licensing transactions to support the development of AEROSURF and our lyophilized KL4 surfactant, including the U.S. If for any reason, our licensee in Asia does not proceed with development of AEROSURF, or if for any reason, we are unable to transfer the financial burden of AEROSURF to strategic partners or licensees in markets outside of Asia, we may determine that it is in our best interest to terminate some or all AEROSURF activity and cease some or all development activities in all markets. Such action could have a material adverse effect on our business, financial condition and results of operations.

Similarly, our strategy currently contemplates that we will seek to out-license rostafuroxin and invest the proceeds in our other core programs. If we are not successful in our efforts, we may be forced to accept a significant write down of our rostafuroxin asset on our balance sheet and reassess our strategy. This action also could have a material adverse effect on our business, financial condition and results of operations.

The execution of a clinical program is complex and involves the cooperation of many individuals and entities, including third parties that we may not be able to control, and require the coordination of a number of components, any one of which could experience delays or unforeseen events or circumstances that may require the development of alternative strategies. If we encounter such events or circumstances, if we believe that certain changes would be in our best interest, we will consider adjusting our strategy and planning. If we conclude that an alternative approach may improve our ability to achieve our objectives, we will consider adopting such other approach. Similarly, if a third party were to share observations or make recommendations concerning the focus, sequence or approach of any or all of our research and development programs, we may consider taking such recommendations into account in our planning process and future activities.

There can be no assurance, whether or not we alter our strategy or plans, that we will be successful, or that we will secure regulatory approval for our product candidates and execute any product launches effectively and on time, if at all, in all markets that we may identify. Our ability to discover and/or develop new product candidates depends in part on our internal research capabilities and whether we have the resources required to conduct a development program or to acquire new product candidates. Our limited resources may not be sufficient to discover and develop or to acquire new product candidates. To support our efforts to develop our product candidates and, if approved, commercialize our products in the world markets, including the U.S., we continue to evaluate potential licensing transactions, collaboration arrangements and other strategic transactions. However, there can be no assurance that our efforts will be successful or that, even if we identify and enter into any strategic transactions, that such transactions will be successfully implemented, if at all, within our expected time frames.

We plan to continue evaluating our business strategy and may modify our strategy again in the future. To respond to changing circumstances, we may expand or alter our research and development activities from time to time and allocate resources to work on development of different products or may pace, delay or halt the development of potential product development programs. As a result of changes in our strategy, we may also change or refocus our existing drug development and manufacturing activities or our plans for commercialization of our product candidates, if approved. These decisions could require changes in our facilities and personnel and restructuring various financial arrangements. There can be no assurances that any product development or other changes that we implement will be successful or that, after implementation of any such changes, that we will not refocus our efforts on new or different objectives.

Our industry is highly competitive, and we have less capital and resources than many of our competitors, which may give them an advantage in developing and marketing products similar to ours or make our product candidates obsolete.

Our industry is highly competitive and subject to rapid technological innovation and evolving industry standards. We compete with numerous existing companies in many ways. We need to successfully introduce new products to achieve our strategic business objectives. If we cannot successfully introduce new products, adapt to changing technologies or anticipate changes in our current and potential customers' requirements, our product candidates may become obsolete and our business could suffer.

Many of our competitors' companies have substantially greater research and development, manufacturing, marketing, financial, and technology personnel and managerial resources than we have. In addition, many of these competitors, either alone or with their collaborative partners, have significantly greater experience than we do in developing products, preclinical testing and human clinical trials management, obtaining FDA approval and other regulatory approvals, and manufacturing and marketing products. Accordingly, our competitors may succeed in receiving FDA or foreign regulatory approval or commercializing products and obtaining patent protection before us. Our competitors may successfully secure regulatory exclusivities in various markets, which could have the effect of barring us or limiting our ability to market our product candidates in such markets. In addition, developments by our competitors may render our drug product candidates obsolete or noncompetitive.

We also face, and will continue to face, competition from colleges, universities, governmental agencies and other public and private research organizations. These competitive forces frequently and aggressively seek patent protection and licensing arrangements to collect royalties for technologies that they develop. Some of these technologies may compete directly with the technologies that we are developing. These institutions will also compete with us in recruiting highly qualified scientific personnel.

The political and healthcare policy and reimbursement environment is becoming more challenging for pharmaceutical companies and medical device manufacturers and may adversely affect our business.

Political, economic and regulatory influences globally are subjecting the healthcare industry to potential fundamental challenges that could substantially affect our business and results of operations. Government and private sector initiatives to limit the growth of healthcare costs, including price regulation, competitive pricing, coverage and payment policies, comparative effectiveness of therapies, technology assessments and managed-care arrangements, are continuing to arise in many countries where we potentially may seek to do business, including the U.S. There is increasing pressure on pricing, reimbursement and demands for value-based data to gain access to patients and healthcare funds globally. This may increase the costs of development, risks of commercialization and overall value of the opportunity. We also cannot predict the likelihood, nature or extent of government regulation that may arise from future legislation, administrative, judicial, or executive action, either in the U.S. or abroad. In addition, we rely on CMOs located in China to manufacture drug product and APIs for us, such that the supply lines for our drug product, and APIs may be affected by trade and political considerations.

Given the increasing uncertainty in the healthcare and pharmaceutical industries as well as increased regulatory scrutiny on foreign investment, capital investment in our industry and our ability to attract capital investment is becoming more challenging. This trend, if continued, may restrict or impair our ability to gain necessary funding for continued development and, if approved, commercialization of our product candidates.

We depend upon key employees and consultants in a competitive market for skilled personnel. If we or our strategic partners or collaborators are unable to attract and retain key personnel, it could adversely affect our ability to develop and market our product candidates.

We have assembled a team of qualified personnel to advance the development programs for our product candidates. We have competed and will continue to compete for qualified individuals with numerous biopharmaceutical companies, universities and other research institutions. Competition for such individuals is significant and attracting and retaining qualified personnel will be critical to our success, and any failure to do so successfully may have a material adverse effect on us.

We are highly dependent upon the members of our executive management team and our directors, as well as our consultants and collaborating scientists. Many of these individuals have been involved with us for many years, have played integral roles in our progress and we believe that they continue to provide value to us. We have over the last few years lost long-term members of our executive team and certain professional, scientific and management personnel, due to retirement, shifts in our focus and other causes. The loss of such personnel potentially exposes us to a lack of ready recall and knowledge of past corporate events, risks previously identified and related learnings. As such, loss of any of our remaining key personnel may further increase the associated risk and may have a material adverse effect on aspects of our business and clinical development and regulatory programs. The loss of services from any of our executives could significantly adversely affect our ability to develop and market our product candidates and obtain necessary regulatory approvals. Further, we do not maintain key man life insurance.

Our future success also will depend on the continued service of our key professional, scientific and management personnel and our ability to recruit and retain additional personnel. While we attempt to provide competitive compensation packages to attract and retain key personnel at all levels in our organization, many of our competitors have greater resources and more experience than we do, making it difficult for us to compete successfully for key personnel. We may experience intense competition for qualified personnel and the existence of non-competition agreements between prospective employees and their former employers may prevent us from hiring those individuals or subject us to lawsuits brought by their former employers.

If our business development activities are unsuccessful, our business could suffer, and our financial performance could be adversely affected.

As part of our long-term growth strategy, we engage in business development activities intended to identify strategic opportunities, including potential strategic alliances, joint development opportunities, acquisitions, technology licensing arrangements and other similar opportunities. Such opportunities may result in substantial investments in our business. Our success in developing product candidates or expanding into new markets from such activities will depend on a number of factors, including our ability to find suitable opportunities for investment, alliance or acquisition; whether we are able to complete an investment, alliance or acquisition on terms that are satisfactory to us; the strength of our underlying technology, product candidates and our ability to execute our business strategies; any intellectual property and litigation related to these product candidates or technology; and our ability to successfully integrate the investment, alliance or acquisition into our existing operations, including to fund our share of any IPR&D projects. If we are unsuccessful in our business development activities, we may be unable to secure needed capital and expertise to support our development programs and our financial condition could be adversely affected.

We may seek to enter into licensing transactions, collaboration arrangements, and other similar transactions and strategic opportunities, and may not be successful in doing so, and even if we are, we may not realize the benefits of such relationships.

We may seek to enter into licensing transactions, collaboration arrangements, and other similar transactions and strategic opportunities for the development or commercialization of our product candidates, or to secure the capital required to develop or commercialize a product candidate or address manufacturing constraints. We may not be successful in our efforts to establish such collaborations for our product candidates because our research and development pipeline may be insufficient, our product candidates may be deemed to be at too early of a stage of development for collaborative effort or third parties may not view our product candidates as having the requisite potential to demonstrate safety and efficacy or significant commercial opportunity. In addition, we face significant competition in seeking appropriate strategic partners, and the negotiation process can be time consuming and complex. Further, any future collaboration agreements may restrict us from entering into additional agreements with potential collaborators. We cannot be certain that, following a strategic transaction or licensing agreement, we will achieve an economic benefit that justifies such transaction.

Even if we are successful in our efforts to establish such collaborations, the terms that we agree upon may not be favorable to us, and we may not be able to maintain such collaborations if, for example, development or approval of a product candidate is delayed, the safety of a product candidate is questioned or sales of an approved product candidate are unsatisfactory.

In addition, any potential future collaborations may be terminable by our strategic partners, and we may not be able to adequately protect our rights under these agreements. Furthermore, strategic partners may negotiate for certain rights to control decisions regarding the development and commercialization of our product candidates, if approved, and may not conduct those activities in the same manner as we do. Any termination of collaborations we enter into in the future, or any delay in entering into collaborations related to our product candidates, could delay the development and commercialization of our product candidates and reduce their competitiveness if they reach the market, which could have a material adverse effect on our business, financial condition and results of operations.

We could be adversely affected by any interruption, including from breaches in cybersecurity, in our ability to conduct business at our current location.

We do not have redundant facilities. We perform substantially all of our research and development and back office activity in a small number of locations, including our headquarters in Warrington, Pennsylvania, research laboratories at Universita degli Studi di Milano-Bicocca, a university in Milan, Italy, which are made available to us under a collaboration agreement with the university, and a research laboratory at Chang Gung University in Taiwan under a separate collaboration agreement. We also depend upon third-party manufacturers and laboratories to manufacture our drug product candidates, APIs and our ADS and perform important API and drug product release testing and stability work.

Our facilities, equipment and inventory would be costly to replace and could require substantial lead time to repair or replace. Our facilities and those of our third-party manufacturers and laboratories may be harmed or rendered inoperable by natural or man-made disasters, including, but not limited to, tornadoes, flooding, fire and power outages, which may render it difficult or impossible for us to perform our research, development and commercialization activities for some period of time. The inability to perform those activities, combined with the time it may take to rebuild our inventory of finished product, may result in the loss of customers or harm to our reputation. Although we have insurance for damage to our property and the disruption of our business, this insurance may not be sufficient to cover all of our potential losses and this insurance may not continue to be available to us on acceptable terms, or at all.

The failure to prevail in litigation or the costs of litigation, including securities class actions, product liability claims and patent infringement claims, could harm our financial performance and business operations.

We are potentially susceptible to litigation. For example, as a public company, we may be subject to claims asserting violations of securities laws. Even if such actions are found to be without merit, the potential impact of such actions, which generally seek unquantifiable damages and attorneys' fees and expenses, is uncertain. There can be no assurance that an adverse result in any future proceeding would not have a potentially material adverse effect on our business, results of operations and financial condition.

Our business activities, including development, manufacture and, if our product candidates are approved, marketing of our drug products and drug/medical device combination products also exposes us to liability risks. Using our drug product candidates or medical devices, including in clinical trials, may expose us to product liability claims. Even if approved, our products may be subject to claims resulting from unintended effects that result in injury or death. Product liability claims alleging inadequate disclosure and warnings in our package inserts and medical device disclosures also may arise.

We presently carry comprehensive general liability, property damage, product liability, workers' compensation, health benefits and other insurance coverage in amounts that we believe to be adequate for the protection of our assets and operations and customary for companies in our industry of comparable size and level of activity. However, our insurance policies contain various deductibles, limitations and exclusions from coverage, and in any event might not fully cover any potential claims. There can be no assurance that the insurance coverage we maintain is sufficient or will be available in adequate amounts or at a reasonable cost. A successful claim brought against us in excess of available insurance or not covered by indemnification agreements, or any claim that results in significant adverse publicity against us, could have an adverse effect on our business and our reputation.

Product liability claims may be brought by individuals or by groups seeking to represent a class. The outcome of litigation, particularly class action lawsuits, is difficult to assess or quantify. Plaintiffs in these types of lawsuits often seek recovery of very large or indeterminate amounts, and the magnitude of the potential loss relating to such lawsuits may remain unknown for substantial periods of time.

We face a potential risk of product liability as a result of the clinical testing of our product candidates and will face an even greater risk if we commercialize any of our product candidates or any other future product. For example, we may be sued if any product we develop, including any of our product candidates, or any materials that we use in our product candidates allegedly causes injury or is found to be otherwise unsuitable during product testing, manufacturing, marketing or sale. Any such product liability claims may include allegations of defects in manufacturing, defects in design, a failure to warn of dangers inherent in the product, negligence, strict liability and a breach of warranties. In the U.S., claims could also be asserted under state consumer protection acts. If we cannot successfully defend ourselves against product liability claims, we may incur substantial liabilities or be required to limit commercialization of our product candidates. Even successful defense would require significant financial and management resources. Regardless of the merits or eventual outcome, liability claims may result in:

- decreased demand for any of our product candidates or any future products that we may develop;
- injury to our reputation;
- withdrawal of clinical trial participants;
- costs to defend the related litigation;
- a diversion of management's time, attention and our resources;
- substantial monetary awards to trial participants or patients;
- product recalls, withdrawals or labeling, marketing or promotional restrictions;
- the inability to commercialize some or all of our product candidates; and
- a decline in the value of our stock.

There can be no assurance that the insurance coverage we maintain is sufficient or will be available in adequate amounts or at a reasonable cost. A successful claim brought against us in excess of available insurance or not covered by indemnification agreements, or any claim that results in significant adverse publicity against us, could have an adverse effect on our business and our reputation.

We may be required to obtain additional product liability insurance coverage. However, such insurance is expensive and may not be available when we need it. In the future, we may not be able to obtain adequate insurance, with acceptable limits and retentions, at an acceptable cost. Any product, general liability or product liability claim, even if such claim is within the limits of our insurance coverage or meritless and/or unsuccessful, could adversely affect the availability or cost of insurance generally and our cash available for other purposes, such as research and development. In addition, such claims could result in:

- uninsured expenses related to defense or payment of substantial monetary awards to claimants;
- a decrease in demand for our drug product candidates;
- damage to our reputation; and
- an inability to complete clinical trial programs or to commercialize our drug product candidates, if approved.

Risks Related to Government Regulation

Our activities are subject to various and complex laws and regulations, and we are susceptible to a changing regulatory environment. Violations or allegations of violations of these laws may result in large civil and criminal penalties, debarment from participating in government programs, diversion of management time, attention and resources and may otherwise have a material adverse effect on our business, financial condition and results of operations.

Our product candidates and our operations are regulated by numerous government agencies, both inside and outside the U.S. Our drug product candidates and medical devices must undergo lengthy and rigorous testing and other extensive, costly and time-consuming procedures mandated by the FDA and foreign regulatory authorities. Our facilities and those of our third-party providers must pass inspection and/or be approved or licensed prior to production and remain subject to inspection at any time thereafter. Failure to comply with the requirements of the FDA or other regulatory authorities could result in warning or untitled letters, product recalls or seizures, monetary sanctions, injunctions to halt the manufacture and distribution of our product candidates, civil or criminal sanctions, refusal of a government to grant approvals or licenses, restrictions on operations or withdrawal of existing approvals and licenses. Any of these actions could damage our reputation and have a material adverse effect on our sales.

If our product candidates are approved for commercial sale, we will be required to comply with not only the requirements of applicable regulators, but also will become subject to various laws regulating the sales, marketing, and distribution of healthcare-related products. The sales and marketing of products and relationships that pharmaceutical and medical device companies have with healthcare providers are under increasing scrutiny by federal, state and foreign government agencies. The FDA and other federal regulators have increased their enforcement activities with respect to the Anti-Kickback Statute, False Claims Act, off-label promotion of products, and other healthcare related laws, antitrust and other competition laws. Foreign governments have also increased their scrutiny of pharmaceutical companies' sales and marketing activities and relationships with healthcare providers.

Of particular importance, federal and state anti-kickback laws make it illegal for a prescription drug manufacturer to solicit, offer, receive, or pay any remuneration in exchange for, or to induce, the referral of business, including the purchase or prescription of a particular drug. These laws can be complicated, are subject to frequent change and may be violated unknowingly. In addition, a number of states require that companies implement compliance programs or comply with industry ethics codes, adopt spending limits, and report to state governments any gifts, compensation, and other remuneration provided to physicians. Sanctions under these laws may include civil monetary penalties, exclusion of a manufacturer's products from reimbursement under government programs (including Medicare and Medicaid), criminal fines, and imprisonment. Companies that have chosen to settle these alleged violations have typically paid multi-million-dollar fines to the government and agreed to abide by corporate integrity agreements, which often include significant and costly burdens.

There has been a recent trend of increased federal and state regulation of payments and transfers of value provided to healthcare professionals and entities. For example, the Physician Payment Sunshine Act imposes annual reporting requirements on certain manufacturers of drugs, medical devices, biologics and medical supplies with respect to payments and other transfers of value provided by them, directly or indirectly, to physicians and teaching hospitals, as well as with respect to certain ownership and investment interests held by physicians and their family members. A manufacturer's failure to submit timely, accurately and completely the required information regarding all payments, transfers of value or ownership or investment interests may result in civil monetary penalties. Certain states also mandate implementation of commercial compliance programs, impose restrictions on medical device manufacturers' marketing practices, and require the tracking and reporting of gifts, compensation and other remuneration to healthcare professionals and entities under certain circumstances.

We are continually evaluating our compliance programs, including policies, training and various forms of monitoring, designed to address the requirements outlined above. However, no compliance program can mitigate risk in its entirety. Violations or allegations of violations of these laws may result in large civil and criminal penalties, debarment from participating in government programs, diversion of management time, attention and resources and may otherwise have a material adverse effect on our business, financial condition and results of operations.

Failure in our information technology systems could disrupt our operations and cause the loss of confidential information and business opportunities.

In the ordinary course of our business, we and our third-party contractors maintain sensitive data on our and their respective networks, including our intellectual property and proprietary or confidential business information relating to our business and that of our clinical trial participants and business partners and electronically stored work product, including clinical data, analyses, research, communications and other materials necessary to gain regulatory approval of our product candidates. The secure maintenance of this sensitive information is critical to our business and reputation. Despite the implementation of security measures, our internal computer systems and those of our third-party contractors are vulnerable to damage from cyber-attacks, computer viruses, unauthorized access, unintended loss, human error, natural disasters, terrorism, war and telecommunication and electrical failures. For information stored with our third-party contractors, we rely upon, and the integrity and confidentiality of such information is dependent upon, the risk mitigation and data preservation efforts such third-party contractors have in place. Our and our third-party contractors' respective network and storage applications and policies may not be sufficient to protect our sensitive business information and may be subject to loss, unauthorized access by hackers or breached due to operator error, malfeasance or other system disruptions. It is often difficult to anticipate or immediately detect such incidents and the damage caused by such incidents. Such incidents could compromise our intellectual property, expose sensitive business information, result in loss of data necessary to secure regulatory approval of our product candidates, cause interruptions in our operations, result in a material disruption of our operations, or require substantial expenditures of resources to remedy.

We face risks related to our collection and use of data, which could result in investigations, inquiries, litigation, fines, legislative and regulatory action and negative press about our privacy and data protection practices.

Our business processes personal data, including some data related to health. When conducting clinical trials, we face risks associated with collecting trial participants' data, especially health data, in a manner consistent with applicable laws and regulations. We also face risks inherent in handling large volumes of data and in protecting the security of such data. We could be subject to attacks on our systems by outside parties or fraudulent or inappropriate behavior by our service providers or employees. Third parties may also gain access to users' accounts using stolen or inferred credentials, computer malware, viruses, spamming, phishing attacks or other means, and may use such access to obtain users' personal data or prevent use of their accounts. Data breaches could subject us to individual or consumer class action litigation and governmental investigations and proceedings by federal, state and local regulatory entities in the U.S. and by international regulatory entities, resulting in exposure to material civil and/or criminal liability. Further, our general liability insurance and corporate risk program may not cover all potential claims to which we are exposed and may not be adequate to indemnify us for all liability that may be imposed.

Our business requires that we and our third-party service providers collect and store sensitive data, including legally protected health information, personally identifiable information about patients, credit card information, and our proprietary business and financial information. As a covered entity, we must comply with the HIPAA privacy and security regulations, which may increase our operational costs. Furthermore, the privacy and security regulations provide for significant fines and other penalties for wrongful use or disclosure of protected health information, or PHI, including potential civil and criminal fines and penalties. We face a number of risks relative to our protection of, and our service providers' protection of, this critical information, including loss of access, fraudulent modifications, inappropriate disclosure and inappropriate access, as well as risks associated with our ability to identify and audit such events. The secure processing, storage, maintenance and transmission of this critical information is vital to our operations and business strategy, and we devote significant resources to protecting such information. Although we take measures to protect sensitive information from unauthorized access or disclosure, our information technology and infrastructure may be vulnerable to attacks by hackers or viruses or otherwise breached due to employee error, malfeasance or other activities. If such event would occur and cause interruptions in our operations, our networks would be compromised and the information we store on those networks could be accessed by unauthorized parties, publicly disclosed, modified without our knowledge, lost or stolen.

Additionally, we share PHI with third-party contractors who are contractually obligated to safeguard and maintain the confidentiality of PHI. Unauthorized persons may be able to gain access to PHI stored in such third-party contractors' computer networks. Any wrongful use or disclosure of PHI by us or our third-party contractors, including disclosure due to data theft or unauthorized access to our or our third-party contractors' computer networks, could subject us to fines or penalties that could adversely affect our business and results of operations. Although the HIPAA statute and regulations do not expressly provide for a private right of damages, we also could incur damages under state laws to private parties for the wrongful use or disclosure of confidential health information or other private personal information by us or our third-party contractors. Unauthorized access, loss, modification or dissemination could disrupt our operations, including our ability to process tests, provide test results, bill payers or patients, process claims, provide customer assistance services, conduct research and development activities, collect, process and prepare company financial information, provide information about our solution and other patient and physician education and outreach efforts through our website, manage the administrative aspects of our business and damage our reputation, any of which could adversely affect our business. In addition, the interpretation and application of consumer, health-related and data protection laws in the U.S. are often uncertain, contradictory and in flux. It is possible that these laws may be interpreted and applied in a manner that is inconsistent with our practices. Complying with these various laws could cause us to incur substantial costs or require us to change our business practices, systems and compliance procedures in a manner adverse to our business.

As our operations and business grow, we may become subject to or affected by new or additional data protection laws and regulations and face increased scrutiny or attention from regulatory authorities, including various domestic and international privacy and security regulations. The legislative and regulatory landscape for privacy and data protection continues to evolve. In the U.S., certain states may adopt privacy and security laws and regulations that may be more stringent than applicable federal law. For example, California enacted the California Consumer Privacy Act, or CCPA, which took effect on January 1, 2020. The CCPA creates individual privacy rights for California consumers and increases the privacy and security obligations of entities handling certain personal data. We may also be subject to data protection laws and regulations of other jurisdictions, such as the EU's General Data Protection Regulation, which provides data subjects with certain rights and requires organizations to adopt technical and organizational safeguards to protect personal data. In the event that we are subject to or affected by privacy and data protection laws, including the CCPA, the EU's General Data Protection Regulation, or GDPR, and other domestic or international privacy and data protection laws, we may expend significant resources to comply with such laws, and any liability from failure to comply with the requirements of these laws could adversely affect our financial condition.

Additionally, we are subject to laws and regulations regarding cross-border transfers of personal data, including laws relating to transfer of personal data outside of the EEA and Switzerland. We rely on transfer mechanisms permitted under these laws, including EU Standard Contract Clauses. If we cannot rely on existing mechanisms for transferring personal data from the EEA, the UK, Switzerland or other jurisdictions, we could be prevented from transferring personal data of patients or employees in those regions, all of which could have a material adverse effect on our business, operating results and prospects.

Healthcare reform measures in the U.S., as well as the general tightening of drug reimbursement pathways and levels of reimbursement globally, are expected to add additional pressure to achieve financial expectations for our product candidates, if approved.

The U.S. and many foreign jurisdictions have enacted or proposed legislative and regulatory changes affecting the healthcare system that may affect our ability to profitably sell our product and product candidates, if approved. The U.S. government, state legislatures and foreign governments also have shown significant interest in implementing cost-containment programs to limit the growth of government-paid healthcare costs, including price controls, restrictions on reimbursement and requirements for substitution of generic products for branded prescription drugs.

The Affordable Care Act was intended to broaden access to health insurance, reduce or constrain the growth of healthcare spending, enhance remedies against fraud and abuse, add transparency requirements for the healthcare and health insurance industries, impose new taxes and fees on the health industry and impose additional health policy reforms.

There have been significant ongoing judicial, administrative, executive and legislative efforts to modify or eliminate the Affordable Care Act. For example, the Tax Act enacted on December 22, 2017, repealed the shared responsibility payment for individuals who fail to maintain minimum essential coverage under section 5000A of the Internal Revenue Code, commonly referred to as the individual mandate. The Trump administration issued executive orders which sought to reduce burdens associated with the Affordable Care Act and modified how it was implemented. Other legislative changes have been proposed and adopted since passage of the Affordable Care Act. The Budget Control Act of 2011, among other things, created the Joint Select Committee on Deficit Reduction to recommend proposals in spending reductions to Congress. The Joint Select Committee did not achieve its targeted deficit reduction of an amount greater than $1.2 trillion for the fiscal years 2012 through 2021, triggering the legislation's automatic reductions to several government programs. These reductions included aggregate reductions to Medicare payments to healthcare providers of up to 2.0% per fiscal year, which went into effect in April 2013. Subsequent litigation extended the 2% reduction, on average, to 2030 unless additional Congressional action is taken. However, pursuant to the Coronavirus Aid, Relief and Economic Security Act, or CARES Act, the 2% Medicare sequester reductions have been suspended from May 1, 2020 through December 31, 2021 due to the COVID-19 pandemic. On January 2, 2013, the American Taxpayer Relief Act was signed into law, which, among other things, reduced Medicare payments to several types of providers, including hospitals, imaging centers and cancer treatment centers, and increased the statute of limitations period for the government to recover overpayments to providers from three to five years.

The Affordable Care Act has also been subject to challenges in the courts. On December 14, 2018, a Texas U.S. District Court Judge ruled that the Affordable Care Act is unconstitutional in its entirety because the "individual mandate" was repealed by Congress. On December 18, 2019, the Fifth Circuit U.S. Court of Appeals held that the individual mandate is unconstitutional and remanded the case to the Texas District Court to reconsider its earlier invalidation of the entire Affordable Care Act. An appeal was taken to the U.S. Supreme Court which heard oral arguments in the case on November 10, 2020. On June 17, 2021, the Supreme Court upheld the Affordable Care Act and dismissed the case.

Further changes to and under the Affordable Care Act remain possible, although the new Biden administration has signaled that it plans to build on the Affordable Care Act and expand the number of people who are eligible for subsidies under it. President Biden indicated that he intends to use executive orders to undo changes to the Affordable Care Act made by the Trump administration and would advocate for legislation to build on the Affordable Care Act. It is unknown what form any such changes or any law proposed to replace the Affordable Care Act would take, and how or whether it may affect our business in the future. We expect that changes to the Affordable Care Act, the Medicare and Medicaid programs, changes allowing the federal government to directly negotiate drug prices and changes stemming from other healthcare reform measures, especially with regard to healthcare access, financing or other legislation in individual states, could have a material adverse effect on the healthcare industry.

Any reduction in reimbursement from Medicare, Medicaid, or other government programs may result in a similar reduction in payments from private payers. The implementation of cost containment measures or other healthcare reforms may prevent us from being able to generate revenue, attain and maintain profitability of our product and product candidates, if approved.

Our international operations subject us to additional regulatory oversight in foreign jurisdictions, as well as economic, social, and political uncertainties, which could cause a material adverse effect on our business, financial position, and operating results.

We are subject to certain risks associated with having assets, both physical and intangible, and operations located in Taiwan and a representative office in Italy. Our activity in Taiwan and Italy are subject to regulatory agencies, such as the Taiwan Food and Drug Administration and the Italian Ministry of Health. Our operations in foreign jurisdictions are conducted by our subsidiary, CVie Therapeutics, Taiwan, which also owns a substantial portion of our intellectual property. Our international operations may be adversely affected by general economic conditions and economic and fiscal policy, including changes in exchange rates and controls, interest rates and taxation policies, and increased government regulation, which could have a material adverse effect on our business, financial position, and operating results. In addition, the impacts of political unrest, including as a result geopolitical tension, such as a deterioration in the relationship between the U.S. and China, including any potential resulting sanctions, export controls, or other restrictive actions that may be imposed by the U.S. and/or other countries against governmental or other entities in, for example, China or Taiwan, also could have an adverse impact on our international operations.

If product liability lawsuits are brought against us, we may incur substantial liabilities and may be required to limit commercialization of our product candidates.

We face an inherent risk of product liability as a result of the clinical trials of our product candidates and will face an even greater risk if we commercialize our product candidates. For example, we may be sued if our product candidates allegedly cause injury or are found to be otherwise unsuitable during product testing, manufacturing, marketing or sale. Any such product liability claims may include allegations of defects in manufacturing, defects in design, a failure to warn of dangers inherent in the product candidate, negligence, strict liability and a breach of warranties. Claims may be brought against us by clinical trial participants, patients or others using, administering or selling products that may be approved in the future. Claims could also be asserted under state consumer protection acts.

If we cannot successfully defend ourselves against product liability claims, we may incur substantial liabilities or be required to limit or cease the commercialization of our product candidates. Even a successful defense would require significant financial and management resources. Regardless of the merits or eventual outcome, liability claims may result in:

- decreased demand for our product candidates;
- injury to our reputation and significant negative media attention;
- withdrawal of clinical trial participants;
- costs to defend the related litigation;
- a diversion of management's time, attention and our resources;
- substantial monetary awards to trial participants or patients;
- product recalls, withdrawals or labeling, marketing or promotional restrictions;
- significant negative financial impact;
- the inability to commercialize our product candidates; and
- a decline in our stock price.

We currently hold product liability insurance coverage at a level we believe to be consistent with our activities. We may need to increase our insurance coverage as we expand our clinical trials or if we commence commercialization of our product candidates. Insurance coverage is increasingly expensive.

Our inability to obtain and retain sufficient product liability insurance at an acceptable cost to protect against potential product liability claims could prevent or inhibit the commercialization of our product candidates. Although we maintain such insurance, any claim that may be brought against us could result in a court judgment or settlement in an amount that is not covered, in whole or in part, by our insurance or that is in excess of the limits of our insurance coverage. Our insurance policies will also have various exclusions, and we may be subject to a product liability claim for which we have no coverage. We may have to pay any amounts awarded by a court or negotiated in a settlement that exceed our coverage limitations or that are not covered by our insurance, and we may not have, or be able to obtain, sufficient capital to pay such amounts.

Our employees and independent contractors, including principal investigators, CROs, consultants and vendors, may engage in misconduct or other improper activities, including noncompliance with regulatory standards and requirements.

We are exposed to the risk that our employees and independent contractors, including principal investigators, CROs, consultants and vendors may engage in misconduct or other illegal activity. Misconduct by these parties could include intentional, reckless and/or negligent conduct or disclosure of unauthorized activities to us that violate: (i) the laws and regulations of the FDA and other similar regulatory requirements, including those laws that require the reporting of true, complete and accurate information to such authorities, (ii) manufacturing standards, including cGMP requirements, (iii) federal and state data privacy, security, fraud and abuse and other healthcare laws and regulations in the U.S. and abroad or (iv) laws that require the true, complete and accurate reporting of financial information or data. Activities subject to these laws also involve the improper use or misrepresentation of information obtained in the course of clinical trials, the creation of fraudulent data in our preclinical studies or clinical trials, or illegal misappropriation of drug product, which could result in regulatory sanctions and cause serious harm to our reputation. It is not always possible to identify and deter misconduct by employees and other third parties, and the precautions we take to detect and prevent this activity may not be effective in controlling unknown or unmanaged risks or losses or in protecting us from governmental investigations or other actions or lawsuits stemming from a failure to be in compliance with such laws or regulations. In addition, we are subject to the risk that a person or government could allege such fraud or other misconduct, even if none occurred. If any such actions are instituted against us, and we are not successful in defending ourselves or asserting our rights, those actions could have a significant impact on our business and financial results, including, without limitation, the imposition of significant civil, criminal and administrative penalties, damages, monetary fines, disgorgements, possible exclusion from participation in Medicare, Medicaid and other federal healthcare programs, individual imprisonment, contractual damages, reputational harm, diminished profits and future earnings, additional reporting requirements and oversight if we become subject to a corporate integrity agreement or similar agreement to resolve allegations of non-compliance with these laws, and curtailment of our operations, any of which could adversely affect our ability to operate our business and our results of operations.

We are subject to anti-bribery, anti-corruption, and anti-money laundering laws, including the U.S. Foreign Corrupt Practices Act, in which violations of these laws could result in substantial penalties and prosecution.

We are exposed to trade and economic sanctions and other restrictions imposed by the U.S. and other governments and organizations. The U.S. Departments of Justice, Commerce, State and Treasury and other federal agencies and authorities have a broad range of civil and criminal penalties they may seek to impose against corporations and individuals for violations of economic sanctions laws, export control laws, the U.S. Foreign Corrupt Practices Act, or the FCPA, and other federal statutes and regulations, including those established by the Office of Foreign Assets Control. The Department of Justice, or DOJ, also has increased its focus on the enforcement of the FCPA, particularly as it relates to the conduct of pharmaceutical companies.

In addition, the U.K. Bribery Act of 2010, or the Bribery Act, prohibits both domestic and international bribery, as well as bribery across both private and public sectors. An organization that "fails to prevent bribery" by anyone associated with the organization can be charged under the Bribery Act unless the organization can establish the defense of having implemented "adequate procedures" to prevent bribery. Under these laws and regulations, as well as other anti-corruption laws, anti-money laundering laws, export control laws, customs laws, sanctions laws and other laws governing our operations, various government agencies may require export licenses, may seek to impose modifications to business practices, including cessation of business activities in sanctioned countries or with sanctioned persons or entities and modifications to compliance programs, which may increase compliance costs, and may subject us to fines, penalties and other sanctions. A violation of these laws or regulations would negatively affect our business, financial condition and results of operations.

We and any of our third-party manufacturers or suppliers may use potent chemical agents and hazardous materials, and any claims relating to improper handling, storage or disposal of these materials could be time consuming or costly.

We and any of our third-party manufacturers or suppliers will use biological materials, potent chemical agents and may use hazardous materials, including chemicals and biological agents and compounds that could be dangerous to human health and safety of the environment. Our operations and the operations of our third-party manufacturers and suppliers also produce hazardous waste products. Federal, state and local laws and regulations govern the use, generation, manufacture, storage, handling and disposal of these materials and wastes. Compliance with applicable environmental laws and regulations may be expensive, and current or future environmental laws and regulations may impair our product development efforts. In addition, we cannot eliminate the risk of accidental injury or contamination from these materials or wastes. We carry a limited amount of specific biological or hazardous waste insurance coverage, and our property, casualty and general liability insurance policies offer limited coverage for damages and fines arising from biological or hazardous waste exposure or contamination. In the event of contamination or injury, we could be held liable for damages or be penalized with fines in an amount exceeding our resources, and our clinical trials or regulatory approvals could be suspended.

Although we maintain workers' compensation insurance for certain costs and expenses we may incur due to injuries to our employees resulting from the use of hazardous materials or other work-related injuries, this insurance may not provide adequate coverage against potential liabilities.

We maintain a limited amount of insurance for toxic tort claims that may be asserted against us in connection with our storage or disposal of biologic, hazardous or radioactive materials.

In addition, we may incur substantial costs in order to comply with current or future environmental, health and safety laws and regulations, which have tended to become more stringent over time. These current or future laws and regulations may impair our research, development or production efforts. Failure to comply with these laws and regulations also may result in substantial fines, penalties or other sanctions or liabilities, which could materially adversely affect our business, financial condition, results of operations and prospects.

Risks Related to Intellectual Property Matters

If we cannot protect our intellectual property, others could use our technology in competitive products. Even if we obtain patents to protect our product candidates, those patents may not be sufficiently broad, or they may expire and others could then compete with us.

The patent position of biotechnology companies is highly uncertain and involves complex legal and factual questions for which important legal principles are unresolved. To date, the U.S. Patent and Trademark Office, or USPTO, has not adopted a consistent policy regarding the breadth of claims that is accorded in biotechnology patents or the degree of protection that these types of patents afford. As a result, there are risks that we may not secure proprietary rights to products or processes that appear to be patentable.

The parties who licensed technologies to us and we have filed various U.S. and foreign patent applications with respect to the products and technologies under our development, and the USPTO and foreign patent offices have issued patents with respect to our products and technologies. These patent applications include international applications filed under the Patent Cooperation Treaty. Our pending patent applications, as well as those we may file in the future or those we may license from third parties, may not result in the USPTO or foreign patent office issuing patents. In addition, if patent rights covering our products are not sufficiently broad, they may not provide us with sufficient proprietary protection or competitive advantages against competitors with similar products and technologies. For example, the core composition of matter patents covering istaroxime have expired. As such, istaroxime relies on data and market exclusivity, as well as method-of-use patents, which may offer a lesser scope of protection than the original core patents. Furthermore, even if the USPTO or foreign patent offices were to issue patents to us or our licensors, others may challenge the patents or circumvent the patents, or the patent office or the courts may invalidate the patents. Thus, any patents we own or license from third parties may not provide us any protection against competitors.

The patents that we own or in-license have a limited life. Patents related to our cardiovascular drug products issued in the U.S., Europe and elsewhere have expired or will expire on various dates between 2028 and 2039.

Intellectual property rights of third parties could limit our ability to develop and market our product candidates.

Our success also depends upon our ability to operate our business without infringing the patents or violating the proprietary rights of others. Patent applications in most jurisdictions are not published until 18 months after filing. In certain cases, the USPTO keeps U.S. patent applications confidential for the entire time the applications are pending. As a result, we cannot determine in advance what inventions third parties may claim in their pending patent applications. We may need to defend or enforce our patent and license rights or to determine the scope and validity of the proprietary rights of others through legal proceedings, which would be costly, unpredictable and time consuming. Even in proceedings where the outcome is favorable to us, they would likely divert substantial resources, including management time, from our other activities. Moreover, any adverse determination could subject us to significant liability or require us to seek licenses that third parties might not grant to us or might only grant at rates that diminish or deplete the profitability of our products. An adverse determination could also require us to alter our products or processes or cease altogether any product sales or related research and development activities.

We may need to license intellectual property from third parties, and such licenses may not be available or may not be available on commercially reasonable terms.

We may need to obtain licenses from third parties to advance our research or allow commercialization of our product candidates, and we cannot provide any assurances that third-party patents do not exist which might be enforced against our product candidates in the absence of such a license. The licensing and acquisition of third-party intellectual property rights is a competitive practice and companies that may be more established, or have greater resources than we do, may also be pursuing strategies to license or acquire third-party intellectual property rights that we may consider necessary or attractive in order to commercialize our product candidates. We may fail to obtain any of these licenses on commercially reasonable terms, if at all. Even if we are able to obtain a license, it may be non-exclusive, thereby giving our competitors access to the same technologies licensed to us. In that event, we may be required to expend significant time and resources to develop or license replacement technology. If we are unable to do so, we may be unable to develop or commercialize the affected product candidates, which could materially harm our business and the third parties owning such intellectual property rights could seek either an injunction prohibiting our sales, or, with respect to our sales, an obligation on our part to pay royalties and/or other forms of compensation. Licensing of intellectual property is of critical importance to our business and involves complex legal, business and scientific issues. If disputes over intellectual property that we have licensed prevent or impair our ability to maintain our current licensing arrangements on acceptable terms, we may not be able to successfully develop and commercialize the affected product candidates, which would have a material adverse effect on our business.

We rely on agreements containing obligations regarding intellectual property, confidentiality and noncompetition provisions that could be breached and may be difficult to enforce.

Although we take what we believe to be reasonable steps to protect our intellectual property, including the use of agreements relating to the non-disclosure of our confidential and proprietary information and trade secrets to third parties, as well as agreements that provide for disclosure and assignment to us of all rights to the ideas, developments, improvements, discoveries and inventions of our employees, consultants, advisors and research collaborators while we employ them, such agreements can be difficult and costly to enforce. We generally seek to enter into these types of agreements with consultants, advisors and research collaborators; however, to the extent that such parties apply or independently develop intellectual property in connection with any of our projects, disputes may arise concerning allocation of the related proprietary rights. Such disputes often involve significant expense and yield unpredictable results.

Moreover, although all employees enter into agreements with us that include non-compete covenants, and our senior executive officers have agreements that include broader non-competition covenants and provide for severance payments that are contingent upon the applicable employee's refraining from competition with us, such non-compete provisions can be difficult and costly to monitor and enforce, such that, if any should resign, we may not be successful in enforcing our noncompetition agreements with them.

Despite the protective measures we employ, we still face the risk that:

- agreements may be breached;
- agreements may not provide adequate remedies for the applicable type of breach;
- our trade secrets or proprietary know-how may otherwise become known;
- our competitors may independently develop similar technology; or
- our competitors may independently discover our proprietary information and trade secrets.

Patents covering our product candidates could be found invalid or unenforceable if challenged in court or before administrative bodies in the U.S. or abroad.

Although an issued patent is presumed valid and enforceable, its issuance is not conclusive as to its validity or its enforceability and it may not provide us with adequate proprietary protection or competitive advantages against competitors with similar product candidates. Competitors could attempt to replicate the competitive advantages we derive from our development efforts, willfully infringe our intellectual property rights, design around the relevant patents, or develop and obtain patent protection for more effective technologies, designs or methods. We may be unable to prevent the unauthorized disclosure or use of our technical knowledge or trade secrets by consultants, suppliers, vendors, former employees and current employees. The laws of some non-U.S. countries do not protect our proprietary rights to the same extent as the laws of the U.S., and we may encounter significant problems in protecting our proprietary rights in these countries.

In addition, proceedings to enforce or defend our patents, or patents to which we have ownership rights through licensing agreements, could put those patents at risk of being invalidated, held unenforceable or interpreted narrowly. Such proceedings could also provoke third parties to assert claims against us, including that some or all of the claims in one or more of those patents are invalid or otherwise unenforceable. If any of the patents covering our product candidates are invalidated or found unenforceable, or if a court found that valid, enforceable patents held by third parties covered one or more of our product candidates, our competitive position could be harmed or we could be required to incur significant expenses to enforce or defend our rights.

Third parties may assert ownership or commercial rights to inventions we develop.

Third parties may in the future make claims challenging the inventorship or ownership of our intellectual property. In addition, we may face claims by third parties that our agreements with employees, contractors or consultants obligating them to assign intellectual property to us are ineffective or in conflict with prior or competing contractual obligations of assignment, which could result in ownership disputes regarding intellectual property we have developed or will develop and interfere with our ability to capture the commercial value of such intellectual property. Litigation may be necessary to resolve an ownership dispute, and if we are not successful, we may be precluded from using certain intellectual property or may lose our exclusive rights in such intellectual property. Either outcome could harm our business and competitive position.

Litigation or other proceedings or third-party claims of intellectual property infringement could require us to spend significant time and money and could prevent us from selling our product candidates or affect our stock price.

Our commercial success will depend in part on not infringing the patents or violating other proprietary rights of others. Significant litigation regarding patent rights occurs in our industry. Our competitors may have applied for or obtained, or may in the future apply for and obtain, patents that will prevent, limit or otherwise interfere with our ability to make, use and sell our product candidates. We do not always conduct independent reviews of patents issued to third parties. In addition, patent applications in the U.S. and elsewhere can be pending for many years before issuance, or unintentionally abandoned patents or applications can be revived, so there may be applications of others now pending or recently revived patents of which we are unaware. Patent applications in the U.S., the EU and elsewhere are published approximately 18 months after the earliest filing for which priority is claimed, with such earliest filing date being commonly referred to as the priority date. These applications may later result in issued patents, or the revival of previously abandoned patents, that will prevent, limit or otherwise interfere with our ability to develop and market our product candidates. Third parties may assert claims that we are employing their proprietary technology without authorization, including claims from competitors or from nonpracticing entities that have no relevant product revenue and against whom our own patent portfolio may have no deterrent effect.

As we attempt to commercialize our product candidates in their current or updated forms, launch new product candidates and enter new markets, we expect competitors may claim that one or more of our product candidates infringe their intellectual property rights as a strategy to impede our commercialization and entry into new markets. The large number of patents, the rapid rate of new patent applications and issuances, the complexities of the technologies involved, and the uncertainty of litigation may increase the risk of business resources and management's attention being diverted to patent litigation. We may in the future receive, letters or other threats or claims from third parties inviting us to take licenses under, or alleging that we infringe, their patents.

Moreover, we may become party to adversarial proceedings regarding our or third-party patent portfolios. Such proceedings could include supplemental examination or contested post-grant proceedings such as review, reexamination, inter parties review, interference or derivation proceedings before the USPTO and challenges in U.S. District Courts. Patents may be subjected to opposition, post-grant review or comparable proceedings lodged in various foreign, both national and regional, patent offices. The legal threshold for initiating litigation or contested proceedings may be low, so that even lawsuits or proceedings with a low probability of success might be initiated. Litigation and contested proceedings can also be expensive and time-consuming, and our adversaries in these proceedings may have the ability to dedicate substantially greater resources to prosecuting these legal actions than we can. We may also occasionally use these proceedings to challenge the patent rights of others. We cannot be certain that any particular challenge will be successful in limiting or eliminating the challenged patent rights of the third party.

Any lawsuits resulting from such allegations could subject us to significant liability for damages and/ or invalidate our proprietary rights. Any potential intellectual property litigation also could force us to do one or more of the following:

- stop making, selling or using product candidates or technologies that allegedly infringe the asserted intellectual property;
- lose the opportunity to license our technology to others or to collect royalty payments;
- incur significant legal expenses, including, in some cases, the attorney's fees and costs of litigation to the party whose intellectual property rights we may be found to be infringing;
- pay substantial damages (possibly treble damages) or royalties to the party whose intellectual property rights on which we may be found to be infringing;
- redesign product candidates that contain the allegedly infringing intellectual property; and
- attempt to obtain a license to the relevant intellectual property from third parties, which may not be available on reasonable terms or at all.

Any litigation or claim against us, even those without merit, may cause us to incur substantial costs, and could place a significant strain on our financial resources, divert the attention of management from our business and harm our reputation. If we are found to infringe the intellectual property rights of third parties, we could be required to pay substantial damages (which may be increased up to three times of awarded damages) and/or substantial royalties and could be prevented from selling our product candidates unless we obtain a license or are able to redesign our product candidates to avoid infringement. Any such license may not be available on reasonable terms, if at all, and there can be no assurance that we would be able to redesign our product candidates in a technically feasible way that would not infringe the intellectual property rights of others. We could encounter delays while we attempt to develop alternative methods or product candidates. If we fail to obtain any required licenses or make any necessary changes to our product candidates or technologies, we may be unable to commercialize one or more of our product candidates.

Even if we were ultimately to prevail, any of these events could require us to divert substantial financial and management resources that we would otherwise be able to devote to our business. Intellectual property litigation, regardless of its outcome, may cause negative publicity, or prohibit us from manufacturing, importing, marketing or otherwise commercializing our product candidates, services and technology. In addition, if the breadth or strength of protection provided by the patents and patent applications we own or in-license is threatened, it could dissuade companies from collaborating with us to license, develop or commercialize current or future product candidates. In addition, because of the substantial amount of discovery required in connection with intellectual property litigation, there is a risk that some of our confidential information could be compromised by disclosure during this type of litigation. There could also be public announcements of the results of hearings, motions or other interim proceedings or developments, and if securities analysts or investors view these announcements in a negative light, the price of our common stock could be adversely affected.

If we are unable to protect the confidentiality of our trade secrets, our business and competitive position could be harmed.

We also rely upon copyright and trade secret protection, as well as non-disclosure agreements and invention assignment agreements with our employees, consultants and third parties, to protect our confidential and proprietary information.

In addition to contractual measures, we try to protect the confidential nature of our proprietary information using commonly accepted physical and technological security measures. Such measures may not provide adequate protection for our proprietary information. Our security measures may not prevent an employee or consultant from misappropriating our trade secrets and providing them to a competitor, and recourse we take against such misconduct may not provide an adequate remedy to protect our interests fully. Unauthorized parties may also attempt to copy or reverse engineer certain aspects of our product candidates that we consider proprietary. Enforcing a claim that a party illegally disclosed or misappropriated a trade secret can be difficult, expensive and time-consuming, and the outcome of any such claim is unpredictable. Trade secret violations are often a matter of state law, and the criteria for protection of trade secrets can vary among different jurisdictions. In addition, trade secrets may be independently developed or reverse engineered by others in a manner that could prevent legal recourse by us. If any of our confidential or proprietary information, such as our trade secrets, were to be disclosed or misappropriated, or if any such information were independently developed by a competitor, our business and competitive position could be harmed.

We may be unable to enforce our intellectual property rights throughout the world.

Filing, prosecuting and defending patents covering our product candidates in all countries throughout the world would be prohibitively expensive, and the laws of some foreign countries do not protect intellectual property rights to the same extent as the laws of the U.S. Many companies have encountered significant problems in protecting and defending intellectual property rights in certain foreign jurisdictions. This could make it difficult for us to stop infringement of our foreign patents, if obtained, or the misappropriation of our other intellectual property rights. For example, some foreign countries have compulsory licensing laws under which a patent owner must grant licenses to third parties. In addition, some countries limit the enforceability of patents against third parties, including government agencies or government contractors. In these countries, patents may provide limited or no benefit. Patent protection must ultimately be sought on a country-by-country basis, which is an expensive and time-consuming process with uncertain outcomes. Accordingly, we may choose not to seek patent protection in certain countries, and we will not have the benefit of patent protection in such countries. Additionally, in the event that our trademarks are successfully challenged, we could be forced to rebrand our product candidates, which could result in loss of brand recognition and could require us to devote resources to advertising and marketing new brands. Our competitors may infringe our trademarks, and we may not have adequate resources to enforce our trademarks.

Proceedings to enforce our patent or trademark rights in foreign jurisdictions could result in substantial costs and divert our efforts and attention from other aspects of our business. Accordingly, our efforts to protect our intellectual property rights in such countries may be inadequate.

Third parties may assert that our employees or consultants have wrongfully used or disclosed confidential information or misappropriated trade secrets.

In the future, we may employ individuals who previously worked with other companies, including our competitors. Although we try to ensure that our employees and consultants do not use the proprietary information or know-how of others in their work for us, we may be subject to claims that we or our employees, consultants or independent contractors have inadvertently or otherwise used or disclosed intellectual property or personal data, including trade secrets or other proprietary information, of a former employer or other third party. Litigation may be necessary to defend against these claims. If we fail in defending any such claims or settling those claims, in addition to paying monetary damages or a settlement payment, we may lose valuable intellectual property rights or personnel. Even if we are successful in defending against such claims, litigation could result in substantial costs and be a distraction to management and other employees.

Changes in U.S. patent laws may limit our ability to obtain, defend and/or enforce our patents.

In 2011, the U.S. enacted and later implemented wide ranging patent reform legislation. The U.S. Supreme Court has ruled on several patent cases since that time, either narrowing the scope of patent protection available in certain circumstances or weakening the rights of patent owners in certain situations. In addition to increasing uncertainty with regard to our ability to obtain patents in the future, this combination of events has created uncertainty with respect to the value of patents, once obtained. Depending on actions by the U.S. Congress, the U.S. federal courts, and the USPTO, the laws and regulations governing patents could change in unpredictable ways that could weaken our ability to obtain new patents or to enforce patents that we have licensed or that we might obtain in the future. Similarly, changes in patent law and regulations in other countries or jurisdictions, changes in the governmental bodies that enforce them or changes in how the relevant governmental authority enforces patent laws or regulations may weaken our ability to obtain new patents or to enforce patents that we have licensed or that we may obtain in the future.

Obtaining and maintaining our patent protection depends on compliance with various procedural, document submission, fee payment and other requirements imposed by governmental patent agencies, and our patent protection could be reduced or eliminated for non-compliance with these requirements.

The USPTO and other patent agencies require compliance with a number of procedural, documentary, fee payment and other similar provisions during the patent application process. In addition, periodic maintenance and annuity fees on any issued patent are due to be paid to the USPTO and other patent agencies over the lifetime of the patent. While an inadvertent failure to make payment of such fees or to comply with such provisions can in many cases be cured by additional payment of a late fee or by other means in accordance with the applicable rules, there are situations in which non-compliance with such provisions will result in the abandonment or lapse of the patent or patent application, and the partial or complete loss of patent rights in the relevant jurisdiction. Non-compliance events that could result in abandonment or lapse of a patent or patent application include failure to respond to official actions within prescribed time limits, non-payment of fees and failure to properly legalize and submit formal documents within prescribed time limits. If we or our licensors fail to maintain the patents and patent applications covering our product or if we or our licensors otherwise allow our patents or patent applications to be abandoned or lapse, it can create opportunities for competitors to enter the market, which would hurt our competitive position and could impair our ability to successfully commercialize our product candidates.

We may be unable to obtain a patent term extension in the U.S. under the Hatch-Waxman Act and in foreign countries under similar legislation.

In the U.S., a patent that covers a drug product or medical device approved by the FDA may be eligible for a term extension designed to restore the period of the patent term that is lost during the premarket regulatory review process conducted by the FDA. Depending upon the timing, duration and conditions of FDA marketing approval of our product candidates, it is possible, though unlikely, that one or more of our U.S. patents may be eligible for limited patent term extension under the Drug Price Competition and Patent Term Restoration Act of 1984, or the Hatch-Waxman Act, which permits a patent term extension of up to five years for a patent covering an approved product as compensation for effective patent term lost during product development and the FDA regulatory review process. A patent term extension cannot extend the remaining term of a patent beyond a total of 14 years from the date of product approval, and only claims covering such approved drug product, a method for using it or a method for manufacturing it may be extended, and only one patent may be extended. In the EU, it is possible, though unlikely, that our product candidates may be eligible for term extensions based on similar legislation. However, in either jurisdiction, if we were eligible to apply for patent term extension, we may not receive an extension if we fail to apply within applicable deadlines, fail to apply prior to expiration of relevant patents or otherwise fail to satisfy applicable requirements. Even if we are granted such extension, the duration of such extension may be less than our request. If we are unable to obtain a patent term extension, or if the term of any such extension is less than our request, the period during which we can enforce our patent rights for that product will be in effect shortened and our competitors may obtain approval to market competing products sooner. The resulting reduction of years of revenue from applicable product candidates could be substantial.

Intellectual property rights do not necessarily address all potential threats.

The degree of future protection afforded by our intellectual property rights is uncertain because intellectual property rights have limitations and may not adequately protect our business or permit us to maintain our competitive advantage. For example:

- others may be able to make products that are similar to our product candidates or utilize similar technology but that are not covered by the claims of our patents or that incorporate certain technology in our product candidates that is in the public domain;
- we, or our future licensors or collaborators, might not have been the first to make the inventions covered by the applicable issued patent or pending patent application that we own now or may own or license in the future;
- we, or our future licensors or collaborators, might not have been the first to file patent applications covering certain of our or their inventions;
- we may not be able to successfully commercialize our product candidates before our relevant patents we may have, or to which we have ownership rights through licensing agreements, expire;
- others may independently develop similar or alternative technologies or duplicate any of our technologies without infringing our intellectual property rights;
- it is possible that our current or future pending patent applications will not lead to issued patents;
- issued patents that we hold rights to may be held invalid or unenforceable, including as a result of legal challenges by our competitors or other third parties;
- our competitors or other third parties might conduct research and development activities in countries where we do not have patent rights and then use the information learned from such activities to develop competitive products for sale in our major commercial markets;
- we may not develop additional proprietary technologies that are patentable;
- the patents of others may harm our business; and
- we may choose not to file a patent in order to maintain certain trade secrets or know-how, and a third party may subsequently file a patent covering such intellectual property.

Any of the foregoing could have a material adverse effect on our business, financial condition and results of operations.

Risks Related to the Ownership of our Securities

The market price of our common stock may be highly volatile, and investors may not be able to resell their shares at or above the price at which they purchase them.

The market price of our common stock, like that of many other development stage pharmaceutical or biotechnology companies, has been and is likely to be volatile. In addition to general economic, political and market conditions, the price and trading volume of our stock could fluctuate widely in response to many factors, including:

- our ability to execute our ongoing and planned clinical trials on a timely basis consistent with timelines established;
- results of our clinical trials and preclinical studies, and the results of trials of our competitors or those of other companies in our market sector;
- regulatory approval of our product candidates, or limitations to specific label indications or patient populations for its use, or changes or delays in the regulatory review process;
- regulatory developments in the U.S. and foreign countries;
- changes in the structure of healthcare payment systems, especially in light of current reforms to the U.S. healthcare system;
- the scope of protection we are able to establish and maintain for intellectual property rights covering our product candidates, along with any product modifications and improvements;
- the success or failure of our efforts to acquire, license or develop additional product candidates;
- innovations or new products developed by us or our competitors;
- announcements by us or our competitors of significant acquisitions, strategic partnerships, joint ventures or capital commitments;
- manufacturing, supply or distribution delays or shortages;
- any changes to our relationship with any manufacturers, suppliers, licensors, future collaborators or other strategic partners;
- our expectations regarding the potential market size and the size of the patient populations for our product candidates;
- the implementation of our business model and strategic plans for our business and technology;
- achievement of expected product sales and profitability;
- variations in our financial results or those of companies that are perceived to be similar to us;
- market conditions in the biopharmaceutical sector and issuance of securities analysts' reports or recommendations;
- trading volume of our common stock;
- an inability to obtain additional funding;
- sales of our stock by insiders and stockholders;
- general economic, industry and market conditions other events or factors, many of which are beyond our control;
- our commercialization, marketing and manufacturing prospects and capabilities;
- additions or departures of key personnel; and
- intellectual property, product liability or other litigation against us.

In addition, the stock markets in general, and the markets for biopharmaceutical and biotechnology stocks in particular, have experienced extreme volatility that may have been unrelated to the operating performance of the issuer. These broad market fluctuations may adversely affect the market price or liquidity of our common stock. In the past, when the market price of a stock has been volatile, holders of that stock have sometimes instituted securities class action litigation against the issuer. If any of our stockholders were to bring such a lawsuit against us, we could incur substantial costs defending the lawsuit and the attention of our management would be diverted from the operation of our business.

The sale and issuance of our common stock or rights to purchase our common stock, stock incentive plans and upon the exercise of outstanding securities exercisable for shares of our common stock, including our AEROSURF warrants, which are exercisable in the future for no consideration, could result in substantial additional dilution of our stockholders, cause our stock price to fall and adversely affect our ability to raise capital.

We will require additional capital to continue to execute our business plan and advance our research and development efforts. To the extent that we raise additional capital through the issuance of additional equity securities and through the exercise of outstanding warrants, our stockholders may experience substantial dilution. We may sell shares of preferred stock or common stock in one or more transactions at prices that may be at a discount to the then-current market value of our common stock and on such other terms and conditions as we may determine from time to time. Any such transaction could result in substantial dilution of our existing stockholders. If we sell shares of our common stock in more than one transaction, stockholders who purchase our common stock may be materially diluted by subsequent sales. Such sales could also cause a drop in the market price of our common stock. The issuance of shares of our common stock in connection with a public or private financing, in connection with our compensation programs, and upon exercise of outstanding warrants will have a dilutive impact on our other stockholders and the issuance, or even potential issuance, of such shares could have a negative effect on the market price of our common stock.

The exercise of stock options and other securities could also cause our stockholders to experience substantial dilution. Moreover, holders of our stock options and warrants are likely to exercise them, if ever, at a time when we otherwise could obtain a price for the sale of our securities that is higher than the exercise price per security of the options or warrants. Such exercises, or the possibility of such exercises, may impede our efforts to obtain additional financing through the sale of additional securities or make such financing more costly. It may also reduce the price of our common stock.

A small group of our investors, including Lee's Holdings, may be able to exercise significant influence over our business strategy and operations.

As of March 31, 2022, Lee's Holdings beneficially owns directly and through its affiliates, approximately 17% of our issued and outstanding shares of common stock and fund affiliates of our Chairman, James Huang, own directly and through affiliates approximately 9% of our issued and outstanding common stock. These investors could exercise their voting power in a coordinated fashion with a limited number of other investors to approve any matter requiring stockholder approval by written consent without a stockholder meeting. As a result, there is a risk that these investors could exert significant influence over the timing, scope, size or ultimate terms of our financing transactions and the process by which such corporate actions are permitted to proceed, or cause corporate actions to be approved even if their interests conflict with the interests of our other stockholders. This concentration of voting power could have the effect of deterring or preventing institutional investors interested in us or a change of control that might be beneficial to our other stockholders.

In addition, affiliates of Lee's Holdings in China serve as CMOs for istaroxime, rostafuroxin and potentially lyophilized KL4 surfactant. As such, we are highly dependent upon their performance to maintain our operational timelines and achieve planned milestones, and as a result, they may be in a position to exert leverage over our planning processes.

Our common stock is listed on the Nasdaq Capital Market. We can provide no assurance that we will be able to comply with the continued listing requirements over time and that our common stock will continue to be listed on the Nasdaq Capital Market.

In May 2020, we successfully listed our common stock on the Nasdaq Capital Market, or Nasdaq. However, we can give no assurance that we will be able to satisfy the continued listing requirements of Nasdaq in the future, including but not limited to the corporate governance requirements and the minimum closing bid price requirement or the minimum equity requirement. If we fail to maintain compliance with the continued listing requirements, Nasdaq may take steps to delist our common stock. If such delisting should occur, it would likely have a negative effect on the price of our common stock and would impair an investor's ability to sell or purchase our common stock when desired. In the event of a delisting, we can provide no assurance that any action taken by us to restore compliance with listing requirements would allow our common stock to become listed again, stabilize the market price or improve the liquidity of our common stock, prevent our common stock from dropping below the Nasdaq minimum bid price requirement or prevent future non-compliance with Nasdaq's listing requirements.

Provisions of our Amended and Restated Certificate of Incorporation, or Certificate of Incorporation, our Amended and Restated By-Laws, or By-Laws, and Delaware law could deter a change of our management and thereby discourage or delay offers to acquire us.

Provisions of our Certificate of Incorporation, our By-Laws and Delaware law may make it more difficult for someone to acquire control of us or for our stockholders to remove existing management and might discourage a third party from offering to acquire us, even if a change of control or in management would be beneficial to our stockholders. Such provisions may make it costlier for a potential acquirer to engage in a business combination transaction with us. Provisions that have the effect of discouraging, delaying or preventing a change of control could limit the opportunity for our stockholders to receive a premium for their shares of our common stock and could also affect the price that some investors are willing to pay for our common stock.

Our Certificate of Incorporation provides that the Court of Chancery of the State of Delaware will be the exclusive forum for substantially all disputes between us and our stockholders, which could limit our stockholders' ability to file in a different judicial forum to resolve disputes with us or our directors, officers or employees.

Our Certificate of Incorporation provides that the Court of Chancery of the State of Delaware is the exclusive forum for any derivative action or proceeding brought on our behalf, any action asserting a breach of fiduciary duty, any action asserting a claim against us arising pursuant to the Delaware General Corporation Law, our Certificate of Incorporation or our By-Laws, or any action asserting a claim against us that is governed by the internal affairs doctrine; provided, that, this provision would not apply to suits brought to enforce a duty or liability created by the Exchange Act. These choice of forum provisions may limit a stockholder's ability to bring a claim in a judicial forum that it finds favorable for disputes with us or our directors, officers or other employees, which may discourage such lawsuits against us and our directors, officers and other employees.

We do not intend to pay dividends on our common stock so any returns will be limited to the value of our stock.

We currently anticipate that we will retain future earnings for the development, operation and expansion of our business and do not anticipate declaring or paying any cash dividends for the foreseeable future. Any return to stockholders will therefore be limited to the appreciation of their stock.

We are a "smaller reporting company," and the reduced disclosure requirements applicable to smaller reporting companies may make our common stock less attractive to investors.

We are a "smaller reporting company" as defined in the Exchange Act and have elected to take advantage of certain of the scaled disclosures available to smaller reporting companies, which include, among other things, audited financial statements and Management Discussion and Analysis for two years instead of three years, an update of the general development of the business for such period that is material to an understanding of the company, simplified executive compensation disclosures, and exemption from the provisions of Section 404(b) of the Sarbanes-Oxley Act requiring that an independent registered accounting firm provide an attestation report on the effectiveness of internal control over financial reporting. We cannot predict whether investors will find our common stock less attractive because of our reliance on any of these exemptions. If some investors find our common stock less attractive as a result, there may be a less active trading market for our common stock and our stock price may be more volatile.

ITEM 1B. UNRESOLVED STAFF COMMENTS.

None.

ITEM 2. PROPERTIES.

We maintain our principal executive offices at 2600 Kelly Road, Suite 100, Warrington, Pennsylvania 18976-3622. Our premises include corporate administration, research and drug development, clinical operations, regulatory affairs, and quality.

We also maintain a location in Taipei, Taiwan consisting of approximately 1,317 square feet of office space, where we oversee certain manufacturing development and preclinical activities occurring at a university in Taiwan related to our cardiovascular drug product candidates. We also have access to research laboratories in Milan, Italy under our collaboration agreement with Universita degli Studi di Milano-Bicocca. We believe our current facilities are adequate for our needs in 2021.

ITEM 3. LEGAL PROCEEDINGS.

We are not aware of any pending legal actions that would, if determined adversely to us, have a material adverse effect on our business and operations.

We may be subject to other legal proceedings and claims in the ordinary course of business. We cannot predict the results of any such disputes, and despite the potential outcomes, the existence thereof may have an adverse material impact on us due to diversion of management time and attention as well as the financial costs related to resolving such disputes.

ITEM 4. MINE SAFETY DISCLOSURES

Not applicable.

PART II

ITEM 5. MARKET FOR REGISTRANT'S COMMON EQUITY, RELATED STOCKHOLDER MATTERS AND ISSUER PURCHASES OF EQUITY SECURITIES.

Market Information

Our common stock is quoted on The Nasdaq Capital Market, or Nasdaq, operated by The Nasdaq Stock Market LLC under the symbol "WINT."

Holders of Our Common Stock

As of March 30, 2022, we had 40 holders of record of shares of our common stock, and there were 28,469,274 shares of our common stock issued and outstanding. The actual number of holders of our common stock is greater than this number of record holders, and includes stockholders who are beneficial owners, but whose shares are held in street name by brokers or held by other nominees. This number of holders of record also does not include stockholders whose shares may be held in trust by other entities.

Dividend Policy

We have not paid any dividends and we do not anticipate paying any cash dividends in the foreseeable future and we intend to retain all of our earnings, if any, to finance our growth and operations and to fund the expansion of our business. Payment of any dividends will be made in the discretion of our Board of Directors, or the Board, after our taking into account various factors, including our financial condition, operating results, current and anticipated cash needs and plans for expansion.

Recent Sales of Unregistered Securities

During the period covered by this Annual Report on Form 10-K, there were no sales by us of unregistered securities that were not previously reported by us in a Quarterly Report on Form 10-Q or Current Report on Form 8-K.

Securities Authorized for Issuance Under Equity Compensation Plans

Information about our equity compensation plans is incorporated herein by reference to Part III, Item 12 of this Annual Report on Form 10-K.

Share Repurchase

We did not purchase any of our registered equity securities during the period covered by this Annual Report on Form 10-K.

ITEM 6. [Reserved].

ITEM 7. MANAGEMENT'S DISCUSSION AND ANALYSIS OF FINANCIAL CONDITION AND RESULTS OF OPERATIONS.

INTRODUCTION

Some of the information contained in this discussion and analysis or set forth elsewhere in this Annual Report on Form 10-K, including information with respect to our plans and strategy for our business and related financing activities, includes forward-looking statements that involve risks and uncertainties. You should review the Forward-Looking Statements and Risk Factors sections of this Annual Report on Form 10-K for a discussion of important factors that could cause actual results to differ materially from the results described in or implied by the forward-looking statements contained in the following discussion and analysis or elsewhere in the Annual Report on Form 10-K.

Management's discussion and analysis of financial condition and results of operations, or MD&A, is provided as a supplement to the accompanying consolidated financial statements and footnotes to help provide an understanding of our financial condition, the changes in our financial condition and our results of operations. This item should be read in connection with our Consolidated Financial Statements for the year ending December 31, 2021 and notes thereto, or Notes, included in this Annual Report on Form 10-K. *See,* Item 8 – Financial Statements and Supplementary Data.

OVERVIEW

We are a clinical-stage biopharmaceutical company focused on the development of novel therapeutics intended to address significant unmet medical needs in important acute care markets. Our development programs are primarily focused in the treatment of acute cardiovascular and secondarily in acute pulmonary diseases. Our lead product candidate, istaroxime, is a first-in-class, dual-acting agent being developed to improve cardiac function in patients with acute heart failure, or AHF, with a potentially differentiated safety profile from existing treatments. Istaroxime demonstrated significant improvement in both diastolic and systolic aspects of cardiac function and was generally well tolerated in two phase 2 clinical trials. Istaroxime has been granted Fast Track designation for the treatment of AHF by the U.S. Food and Drug Administration, or FDA. Based on the profile observed in our phase 2 clinical studies in AHF, where istaroxime significantly improved cardiac function and systolic blood pressure in acute decompensated heart failure patients, we initiated a phase 2 global clinical study to evaluate istaroxime for the treatment of early cardiogenic shock (Society for Cardiovascular Angiography and Interventions Stage B shock), a severe form of heart failure characterized by very low blood pressure and risk for hypoperfusion to critical organs. We believe that istaroxime has the potential to fulfill an unmet need in early cardiogenic shock. Our heart failure cardiovascular portfolio also includes sarco endoplasmic reticulum Ca2+ -ATPase 2a, or SERCA2a, activators which activate SERCA2a. This research program is evaluating these preclinical product candidates, including oral and intravenous SERCA2a activator heart failure compounds. As potential oral agents, these candidates would be developed for chronic heart failure. In addition, our cardiovascular drug product candidates include rostafuroxin, a novel product candidate for the treatment of hypertension in patients with a specific genetic profile. We are pursuing potential licensing arrangements and/or other strategic partnerships and do not intend to advance this product candidate without securing such an arrangement or partnership.

Our pulmonary product candidate portfolio consists of a KL4 surfactant platform to address a range of serious respiratory conditions in children and adults. KL4 surfactant has been in development as a liquid instillate for noninvasive delivery as an aerosol. In September 2020, the FDA accepted our investigational new drug, or IND, application for an open-label phase 2 pilot study to assess safety and tolerability in the COVID-19 acute respiratory distress syndrome, or ARDS, population and the ability of our KL4 surfactant liquid instillate to impact key respiratory parameters in the treatment of lung injury and ARDS resulting from severe acute respiratory syndrome coronavirus 2, or SARS-CoV-2, the causative agent in novel coronavirus, or COVID-19, infections. In January 2022, we completed enrollment of 20 patients in our phase 2 study of lucinactant (KL4 surfactant) for patients with severe COVID-19 associated ARDS and lung injury. The study demonstrated that intratracheal administration of reconstituted lyophilized lucinactant was generally safe and well tolerated. Lucinactant was safely administered to critically ill, mechanically ventilated patients with severe COVID-19 associated ARDS. Oxygenation and other physiological parameters were stable to improved after dosing, supporting the feasibility of this treatment approach to develop a potential treatment for critically ill patients with ARDS due to COVID-19 or other causes.

Previously, we were also developing AEROSURF (lucinactant for inhalation), a novel drug/medical device combination product for noninvasive delivery of aerosolized KL4 surfactant using our ADS technology for the treatment of respiratory distress syndrome, or RDS, in premature infants. We suspended all internal AEROSURF clinical activities in November 2020, because istaroxime, our lead product candidate, has become our primary focus for investment and execution as we believe development of istaroxime represents a greater value opportunity for us and our stockholders than development of KL4 surfactant. Since completing our phase 2 study of lucinactant (KL4 surfactant) for patients with severe COVID-19 associated ARDS and lung injury in January 2022, in order to preserve resources for the highest priority programs, we have begun to reduce costs that were not already transferred to our licensee in Asia, Lee's Pharmaceutical (HK) Ltd., or Lee's (HK), under the terms of our License, Development and Commercialization Agreement between us and Lee's (HK) dated as of June 12, 2017, as amended, or the Asia License Agreement. These costs include certain reductions in headcount dedicated to KL4 surfactant and the decommissioning of both our analytical and technical support laboratory, which previously conducted release testing of active pharmaceutical ingredients, or APIs, and supportive research for our lyophilized and aerosolized KL4 surfactant, and our medical device development laboratory, which was previously used to conduct development activities and testing for our ADS technologies. To support the future development of our KL4 surfactant platform in markets outside of Asia, including the U.S., we are pursuing one or more licensing transactions.

Our ability to advance our development programs is dependent upon our ability to secure additional capital in both the near and long-term, through public or private equity offerings; through potential strategic opportunities, including licensing agreements, drug product development and marketing collaboration arrangements, pharmaceutical research cooperation arrangements or other similar transactions in geographic markets, including the U.S., and/or through potential grants and other funding commitments from U.S. government agencies, in each case, if available. We have engaged with potential counterparties in various markets and will continue to pursue non-dilutive sources of capital as well as potential private and public offerings. There can be no assurance, however, that we will be able to identify and enter into public or private securities offerings on acceptable terms and in amounts sufficient to meet our needs or qualify for non-dilutive funding opportunities under any grant programs sponsored by U.S. government agencies, private foundations and/or leading academic institutions, or identify and enter into any strategic transactions that will provide the additional capital that we will require. If none of these alternatives is available, or if available, we are unable to raise sufficient capital through such transactions, we potentially could be forced to limit or cease our development activities, which would have a material adverse effect on our business, financial condition and results of operations.

We have incurred operating losses since our incorporation on November 6, 1992. For the years ended December 31, 2021 and 2020, we had operating losses of $77.3 million and $30.3 million, respectively. As of December 31, 2021, we had an accumulated deficit of $785.3 million. To date, we have financed our operations primarily through private placements and public offerings of our common and preferred stock and borrowings from investors and financial institutions.

We expect to continue to incur significant research and clinical development, regulatory and other expenses as we (i) continue to develop our product candidates; (ii) seek regulatory clearances or approvals for our product candidates; (iii) conduct clinical trials on our product candidates; and (iv) manufacture, market and sell any product candidates for which we may obtain regulatory approval.

As a result, we will need additional financing to support our continuing operations. Until such time that we can generate substantial product revenues, if ever, we expect to finance our operations through public or private equity offerings; through potential strategic opportunities, including licensing agreements, drug product development and marketing collaboration arrangements, pharmaceutical research cooperation arrangements or other similar transactions in geographic markets outside of Asia, including the U.S.; and/or through potential grants and other funding commitments from U.S. government agencies, in each case, if available. There can be no assurance, however, that we will be able to identify and enter into public or private securities offerings on acceptable terms and in amounts sufficient to meet our needs, or qualify for non-dilutive funding opportunities under any grant programs sponsored by U.S. government agencies, private foundations and/or leading academic institutions, or identify and enter into any strategic transactions that will provide the additional capital that we will require. If none of these alternatives is available, or if available, we are unable to raise sufficient capital through such transactions, we potentially could be forced to limit or cease our development activities, which would have a material adverse effect on our business, financial condition and results of operations.

RESULTS OF OPERATIONS

Comparison of Years Ended December 31, 2021 and 2020

Net Loss and Operating Loss

The operating loss for the years ended December 31, 2021 and 2020 was $77.3 million and $30.3 million, respectively. The increase in operating loss from 2020 to 2021 was due to a $45.0 million non-cash loss on impairment of intangible assets and a $1.9 million increase in combined research and development and general and administrative expenses, which includes a $1.2 million increase in non-cash stock compensation expense and $0.5 million of non-cash expense related to equity consideration for a financial advisory service agreement.

The net loss for the years ended December 31, 2021 and 2020 was $67.6 million, or $2.73 basic net loss per common share, and $32.6 million, or $2.08 basic net loss per common share, respectively. Included in the net loss is (i) a $45.0 million non-cash loss on impairment of intangible assets in 2021; (ii) a deferred income tax benefit of $10.0 million related to the reduction of the deferred tax liability in 2021; (iii) $1.1 million in non-cash expense related to the modification of certain warrants in 2020; (iv) $0.3 million and $1.2 million in foreign currency losses in 2021 and 2020, respectively; and (v) interest expense of $0.1 million for both 2021 and 2020.

Research and Development Expenses

Our research and development expenses are charged to operations as incurred and we incur both direct and indirect expenses for each of our programs. We track direct research and development expenses by preclinical and clinical programs, which include third-party costs such as contract research organization, consulting and clinical trial costs. We do not allocate indirect research and development expenses, which include product development and manufacturing expenses and clinical, medical and regulatory operations expenses, to specific programs. We also account for research and development and report annually by major expense category as follows: (i) contracted services; (ii) salaries and benefits; (iii) stock-based compensation; (iv) raw materials, aerosol devices and supplies; (v) royalties; (vi) rents and utilities; (vii) depreciation; (viii) travel; and (ix) other. We expect to increase our investment in research and development in order to advance our product candidates through additional clinical trials. As a result, we expect that our research and development expenses will increase throughout the foreseeable future as we pursue clinical development of istaroxime and our other current and future product candidates. At this time, we cannot reasonably estimate or know the nature, timing and estimated costs of the efforts that will be necessary to complete the development of our product candidates. We are also unable to predict when, if ever, material net cash inflows will commence from sales of our product candidates.

Research and development expenses for the years ended December 31, 2021 and 2020 are as follows:

(in thousands)	Year Ended December 31, 2021	2020
Istaroxime - early cardiogenic shock	$ 3,236	$ 1,813
Istaroxime - AHF	1,551	966
KL4 surfactant	1,037	1,583
Preclinical studies	6	42
Total direct clinical and preclinical programs	5,830	4,404
Product development and manufacturing	4,360	4,474
Clinical, medical and regulatory operations	7,597	6,495
Total research and development expenses	$ 17,787	$ 15,373

Research and development expenses include non-cash charges associated with stock-based compensation and depreciation of $3.1 million and $2.2 million for 2021 and 2020, respectively.

Direct Clinical and Preclinical Programs

Direct clinical and preclinical development programs include: (i) activities associated with conducting clinical trials, including patient enrollment costs, clinical site costs, clinical device and drug supply, and related external costs, such as consultant fees and expenses; and (ii) development activities, toxicology studies and other preclinical studies.

Total direct clinical and preclinical development programs expenses increased $1.4 million from 2020 to 2021 primarily due to (i) an increase of $1.4 million for ongoing clinical studies of istaroxime for early cardiogenic shock; (ii) an increase of $0.6 million for our continued development of istaroxime for AHF; partially offset by (iii) a decrease of $0.5 million for costs associated with KL4 surfactant.

Product Development and Manufacturing

Product development and manufacturing includes (i) manufacturing operations, with our CMO, validation activities, quality assurance and analytical chemistry capabilities that support the manufacture of our drug products used in research and development activities, and our medical devices, including our ADS, (ii) design and development activities related to our ADS; and (iii) pharmaceutical and manufacturing development activities of our drug product candidates including development of istaroxime. These costs include employee expenses, facility-related costs, depreciation, costs of drug substances (including raw materials), supplies, quality control and assurance activities, analytical services, and expert consultants and outside services to support pharmaceutical and device development activities.

Product development and manufacturing expenses decreased $0.1 million from 2020 to 2021.

Clinical, Medical and Regulatory Operations

Clinical, medical and regulatory operations include (i) medical, scientific, preclinical and clinical, regulatory, data management and biostatistics activities in support of our research and development programs; and (ii) medical affairs activities to provide scientific and medical education support for our KL4 surfactant. These costs include personnel, expert consultants, outside services to support regulatory and data management, symposiums at key medical meetings, facilities-related costs, and other costs for the management of clinical trials.

Clinical, medical and regulatory operations expenses increased $1.1 million from 2020 to 2021 due to an increase of $0.6 million in personnel costs and employee-related incentive bonus expense and an increase of $0.5 million in non-cash, stock compensation expense.

Research and Development Expense by Major Expense Category

We also account for our research and development expense by major expense category as shown in the following table:

(in thousands)	Year Ended December 31, 2021	2020
Contracted services	$ 8,116	$ 5,737
Salaries and benefits	4,906	4,768
Stock-based compensation	2,940	2,098
Royalties	800	800
Rents and utilities	541	503
Depreciation	149	145
Raw materials, aerosol devices and supplies	85	915
Travel	30	28
Other	220	379
	$ 17,787	$ 15,373

Contracted services include third-party costs of preclinical studies, clinical trial activities, certain components of our manufacturing operations, quality control and analytical stability and release testing of our drug products, consulting services, aerosol device design and engineering services, etc. The increase of $2.4 million from 2020 to 2021 is due to an increase in contracted research and clinical trials expense in 2021, primarily related to ongoing clinical studies of istaroxime for early cardiogenic shock and our continued development of istaroxime for AHF.

The decrease in raw materials, aerosol devices and supplies of $0.8 million from 2020 to 2021 is due to a $0.4 million purchase of KL4 surfactant raw materials during 2020 and a decrease in costs associated with our phase 2b bridging study as we ceased enrollment in the study in November 2020.

Royalties represent minimum royalties due under our licensing agreements with Philip Morris USA Inc. and Philip Morris Products S.A. for our ADS technology.

Other consists primarily of ongoing research and development costs such as insurance, taxes, education and training, and software licenses.

Research and Development Projects

A substantial portion of our cumulative losses to date relate to investments in our research and development projects, for which we incurred $33.2 million in expenses for the two-year period ended December 31, 2021. Due to the significant risks and uncertainties inherent in the clinical development and regulatory approval processes, the nature, timing and costs of the efforts necessary to complete individual projects in development are not reasonably estimable. With every phase of a development project, there are unknowns that may significantly affect cost projections and timelines. In view of the number and nature of these factors, many of which are outside our control, the success, timing of completion and ultimate cost of development of any of our product candidates are highly uncertain and cannot be estimated with any degree of certainty. In addition to the risks and uncertainties affecting our research and development projects discussed in this MD&A (*see*, Item 1A – Risk Factors), other risks could arise that we may not foresee that could affect our ability to estimate projections and timelines.

Ultimately, if we do not successfully develop and gain marketing approval for our drug product candidates, in the U.S. or elsewhere, we will not be able to commercialize, or generate any revenues from the sale of our products and the value of our company and our financial condition and results of operations will be substantially harmed.

General and Administrative Expenses

(in thousands)	Year Ended December 31, 2021	2020
General and administrative expenses	$ 14,473	$ 14,944

General and administrative expenses consist of costs for executive management, business development, intellectual property, finance and accounting, legal, human resources, information technology, facility, and other administrative costs.

General and administrative expenses include non-cash charges associated with stock-based compensation of $4.3 million and $3.6 million, respectively, for the years ended December 31, 2021 and 2020. General and administrative expenses decreased $0.5 million from 2020 to 2021 due to (i) a decrease of $0.8 million in severance costs; and (ii) a decrease of $0.4 million in personnel costs; partially offset by (iii) an increase of $0.7 million in non-cash, stock compensation expense.

Other (Expense) Income, Net

(in thousands)	Year Ended December 31, 2021	2020
Interest income	$ 91	$ 122
Interest expense	(114)	(125)
Other expense, net	(320)	(2,246)
Total other expense, net	$ (343)	$ (2,249)

Interest Income

Interest income relates to income on our money market account and U.S. Treasury notes.

Interest expense

Interest expense in 2021 consists of interest expense associated with the loans payable. Interest expense in 2020 consists of interest expense associated with the loans payable and the collaboration and device development payables.

Other expense, net

Other expense, net in 2021 primarily consists of $0.3 million in losses on foreign currency translation. Other expense, net in 2020 primarily consists of $1.2 million in losses on foreign currency translation and $1.1 million in non-cash expense related to the modification of certain warrants.

LIQUIDITY AND CAPITAL RESOURCES

We are subject to risks common to companies in the biotechnology industry, including but not limited to, the need for additional capital, risks of failure of preclinical and clinical studies, the need to obtain marketing approval and reimbursement for any drug product candidate that we may identify and develop, the need to successfully commercialize and gain market acceptance of our product candidates, dependence on key personnel, protection of proprietary technology, compliance with government regulations, development of technological innovations by competitors, and risks associated with our international locations and activities abroad, including but not limited to having foreign suppliers, manufacturers and clinical sites in support of our development activities.

We have incurred net losses since inception. Our net loss was $67.6 million and $32.6 million, respectively, for the years ended December 31, 2021 and 2020. Included in our net loss for the year ended December 31, 2021 is a $45.0 million loss on impairment of intangible assets related to rostafuroxin and a related $10.0 million deferred income tax benefit (*see*, Note 4 – Accounting Policies and Recent Accounting Pronouncements). We expect to continue to incur operating losses for at least the next several years. As of December 31, 2021, we had an accumulated deficit of $785.3 million. Our future success is dependent on our ability to fund and develop our product candidates, and ultimately upon our ability to attain profitable operations. We have devoted substantially all of our financial resources and efforts to research and development and general and administrative expense to support such research and development. Net losses and negative cash flows have had, and will continue to have, an adverse effect on our stockholders' equity and working capital, and accordingly, our ability to execute our future operating plans.

In March 2021, we received net proceeds of approximately $27.4 million related to a public offering of 9,230,500 units at a price per unit of $3.25. Each unit consisted of one share of our common stock and a warrant to purchase one share of common stock, or the March 2021 Warrants. The March 2021 Warrants were immediately exercisable for shares of common stock at a price of $3.60 per share and expire five years from the date of issuance.

We are party to an At-The-Market Offering Agreement with Ladenburg Thalmann & Co. Inc., or Ladenburg, pursuant to which we may offer and sell, from time to time at our sole discretion, up to a maximum of $10.0 million of shares of our common stock through Ladenburg as agent and/or principal through an at-the-market program, or the ATM Program. For the year ended December 31, 2021, we sold 2,116,944 shares of our common stock under the ATM Program resulting in aggregate gross proceeds to us of approximately $5.0 million and net proceeds of approximately $4.8 million (s*ee,* Note 10 – Stockholders' Equity).

As of December 31, 2021, we had cash and cash equivalents of $22.3 million and current liabilities of $4.9 million. As of March 31, 2022, we believe that we have sufficient resources available to support our development activities and business operations and satisfy our obligations into the first quarter of 2023. We do not have sufficient cash and cash equivalents as of the date of this Annual Report on Form 10-K to support our operations for at least the 12 months following the date that the financial statements are issued. These conditions raise substantial doubt about our ability to continue as a going concern through 12 months after the date that the financial statements are issued.

To alleviate the conditions that raise substantial doubt about our ability to continue as a going concern, management plans to secure additional capital, potentially through a combination of public or private equity offerings and strategic transactions, including potential licensing arrangements, alliances and drug product collaborations focused on specified geographic markets; however, none of these alternatives are committed at this time. There can be no assurance that we will be successful in obtaining sufficient funding on terms acceptable to us to fund continuing operations, if at all, or identify and enter into any strategic transactions that will provide the capital that we will require. If none of these alternatives is available, or if available, we are unable to raise sufficient capital through such transactions, we will not have sufficient cash resources and liquidity to fund our business operations for at least the next 12 months following the date that the financial statements are issued. The failure to obtain sufficient capital on acceptable terms when needed would have a material adverse effect on our business, results of operations, and financial condition. Accordingly, management has concluded that substantial doubt exists with respect to our ability to continue as a going concern through 12 months after the issuance of the accompanying financial statements.

The accompanying financial statements have been prepared on a going concern basis, which contemplates the realization of assets and satisfaction of liabilities in the normal course of business, and do not include any adjustments relating to recoverability and classification of recorded asset amounts or the amounts and classification of liabilities that might be necessary should we be unable to continue as a going concern.

Cash Flows

Cash flows for the years ended December 31, 2021 and 2020

Net cash outflows for 2021 consist of $23.7 million net cash used in operating activities, $0.3 million of net cash used in investing activities, and $29.4 million of net cash provided by financing activities.

Operating Activities

Net cash used in operating activities was $23.7 million for the year ended December 31, 2021 and consisted primarily of (i) a net loss of $67.6 million, (ii) a non-cash deferred income tax benefit of $10.0 million, partially offset by (iii) a non-cash loss on impairment of intangible assets of $45.0 million, (iv) non-cash stock-based compensation of $7.2 million, (v) non-cash expense related to equity consideration for a financial advisory service agreement of $0.5 million, (vi) non-cash lease expense of $0.7 million, (vii) an unrealized loss on foreign exchange rate changes of $0.4 million, (viii) changes in operating assets and liabilities of $0.1 million, and (ix) depreciation and amortization of $0.2 million. Changes in prepaid expenses and other current assets, accounts payable, accrued expenses and operating lease liabilities result from timing differences between the receipt and payment of cash and when the transactions are recognized in our results of operations.

Investing Activities

Net cash used in investing activities was $0.3 million for each of the years ended December 31, 2021 and 2020. The net cash used in investing activities is due to $0.3 million in purchases of property and equipment in both 2021 and 2020.

Financing Activities

Net cash provided by financing activities was $29.4 million and $20.0 million for the years ended December 31, 2021 and 2020, respectively, summarized as follows:

(in thousands)	Year Ended December 31, 2021	2020
Proceeds from issuance of common stock and warrants, net of issuance costs	$ 27,390	$ 20,246
Proceeds from ATM Program, net of expenses	4,843	-
Proceeds from research and development funding arrangement	1,000	2,800
Proceeds from exercise of common stock warrants	-	141
Principal payments on loans payable	(3,872)	(3,229)
Proceeds from Paycheck Protection Program loan	-	547
Principal payments on Paycheck Protection Program loan	-	(547)
Net cash provided by financing activities	$ 29,361	$ 19,958

The following sections provide a more detailed discussion of our available financing facilities.

Financings Pursuant to Common Stock Offerings

Historically, we have funded, and expect that we will continue to fund, our business operations through various sources, including financings in the form of common stock offerings. In September 2020, we filed with the SEC a "shelf" registration statement on Form S-3 (No. 333-248874), or the 2020 Universal Shelf, that was declared effective on September 29, 2020, for the proposed offering from time to time of up to $75.0 million of our securities, including common stock, preferred stock, debt securities, warrants, units, subscription rights, or any combination of the foregoing, on terms and conditions that will be determined at the time of an offering. As of December 31, 2021, approximately $1.8 million remained available under the 2020 Universal Shelf. The 2020 Universal Shelf will expire upon the earlier to occur of (i) the sale of $75.0 million of our securities or (ii) September 29, 2023.

In December 2021, we filed with the SEC a "shelf" registration statement on Form S-3 (No. 333-261878), or the 2022 Universal Shelf, that was declared effective on January 3, 2022, for the proposed offering from time to time of up to $100.0 million of our securities, including common stock, preferred stock, debt securities, warrants, units, subscription rights, or any combination of the foregoing, on terms and conditions that will be determined at the time of an offering. The 2022 Universal Shelf will expire upon the earlier to occur of (i) the sale of $100.0 million of our securities or (ii) January 3, 2025. We have not yet made any offerings or sales of our securities under the 2022 Universal Shelf.

At-The-Market Program

On September 17, 2020, we entered into an At-The-Market Offering Agreement with Ladenburg Thalmann & Co. Inc., or Ladenburg, pursuant to which we may offer and sell, from time to time at our sole discretion, up to a maximum of $10.0 million of shares of our common stock through Ladenburg as agent and/or principal through an at-the-market program, or the ATM Program. When we issue sales notices to Ladenburg, we designate the maximum amount of shares to be sold by Ladenburg daily and the minimum price per share at which shares may be sold. Ladenburg may sell shares by any method permitted by law deemed to be an "at-the-market offering" as defined in Rule 415(a)(4) under the Securities Act, or in privately negotiated transactions.

For the year ended December 31, 2021, we sold 2,116,944 shares of our common stock under the ATM Program resulting in aggregate gross proceeds to us of approximately $5.0 million and net proceeds of approximately $4.8 million (*see,* Note 10 – Stockholders' Equity).

As of March 31, 2022, approximately $5.0 million remains available under the ATM Program.

March 2021 Public Offering

On March 23, 2021, we entered into an underwriting agreement with Oppenheimer & Co. Inc. as representative for the several underwriters named therein, relating to a public offering, or the March 2021 Offering, of an aggregate of 9,230,500 units with each unit consisting of one share of common stock and a warrant, or the March 2021 Warrants. The March 2021 Warrants were immediately exercisable for shares of common stock at a price of $3.60 per share and expire five years from the date of issuance. The shares of common stock and the March 2021 Warrants were immediately separable and were issued separately in the March 2021 Offering.

The closing of the March 2021 Offering occurred on March 25, 2021. The offering price to the public was $3.25 per unit resulting in gross proceeds to us of $30.0 million. After deducting underwriting discounts and commissions and estimated offering expenses payable by us, and excluding the proceeds, if any, from the exercise of the March 2021 Warrants issued pursuant to the March 2021 Offering, the net proceeds to us were approximately $27.4 million.

May 2020 Public Offering

On May 20, 2020, we entered into an underwriting agreement, or the Underwriting Agreement, with Ladenburg as representative for the several underwriters named therein, or collectively, the Underwriters, relating to a public offering, or the May 2020 Offering, of an aggregate of 2,758,620 units with each unit consisting of one share of our common stock and a warrant, or the May 2020 Warrants. The May 2020 Warrants were immediately exercisable for shares of common stock at a price of $7.975 per share and expire five years from the date of issuance. The shares of common stock and the May 2020 Warrants were immediately separable and were issued separately in the May 2020 Offering.

In addition, we granted the Underwriters a 45-day option, or the Overallotment Option, to purchase up to 413,793 additional shares of common stock and/or May 2020 Warrants to purchase up to 413,793 additional shares of common stock, which such Overallotment Option was exercised in full.

The closing of the May 2020 Offering occurred on May 22, 2020, inclusive of the Overallotment Option. The offering price to the public was $7.25 per unit. After deducting underwriting discounts and commissions and offering expenses of $2.8 million payable by us, and excluding the proceeds, if any, from the exercise of the May 2020 Warrants issued pursuant to the May 2020 Offering, the net proceeds to us were approximately $20.2 million.

Loans Payable

Current Portion

Loan Payable to Bank Direct Capital Finance

In June 2020, we entered into an insurance premium financing and security agreement with Bank Direct Capital Finance, or Bank Direct. Under the agreement, we financed $1.1 million of certain premiums at a 4.26% annual interest rate. Payments of approximately $117,000 were due monthly from July 2020 through March 2021. As of December 31, 2020, the outstanding principal of the loan was $0.4 million. The balance of the loan was repaid during the first quarter of 2021.

In June 2021, we entered into an insurance premium financing and security agreement with Bank Direct. Under the agreement, we financed $1.3 million of certain premiums at a 3.37% annual interest rate. Payments of approximately $147,000 are due monthly from July 2021 through March 2022. As of December 31, 2021, the outstanding principal of the loan was $0.3 million.

Non-Current Portion

O-Bank Co., Ltd. Credit Facility

In September 2016, CVie Therapeutics entered into a 12-month revolving credit facility of approximately $2.9 million with O-Bank Co., Ltd., or O-Bank, to finance operating activities, or the O-Bank Facility. The O-Bank Facility was later renewed and increased to approximately $5.8 million in September 2017. The O-Bank Facility is guaranteed by Lee's Pharmaceutical Holdings Limited, or Lee's Holdings, which pledged bank deposits in the amount of 110% of the actual borrowing amount. Interest, payable in cash on a monthly basis, was determined based on the 90-day Taipei Interbank Offer Rate, or TAIBOR, plus 0.91%. The O-Bank Facility expired on September 11, 2019 and the loans were set to mature six months after the expiration date, on March 11, 2020. In March 2020, the O-Bank Facility was amended, among other things, to extend the maturity date to March 2022, to decrease the total amount of the O-Bank Facility to approximately $5.0 million, to change the applicable interest rate to the TAIBOR plus 1.17% and to adjust the term to 24-month non-revolving.

In the second quarter of 2020, we were informed by Lee's Holdings of their desire to reduce the amount of pledged bank deposits with O-Bank by 50%. To remain in compliance with the terms of the O-Bank Facility, we repaid approximately $2.3 million of the outstanding principal in August 2020. In November 2020, Lee's Holdings committed to maintain the required level of pledged bank deposits with O-Bank through the date of full repayment of the O-Bank Facility. In June 2021, we repaid the remaining outstanding principal of the O-Bank Facility of approximately $2.5 million.

As of December 31, 2020, the outstanding principal of the O-Bank Facility was approximately $2.4 million and was classified as loans payable - non-current portion. There was no outstanding principal balance as of December 31, 2021, and the O-Bank Facility is no longer available to us.

Restructured Debt Liability

On October 27, 2017, we and Deerfield Management Company, L.P., or Deerfield, entered into the Exchange and Termination Agreement pursuant to which (i) promissory notes evidencing a loan with affiliates of Deerfield Management Company L.P., or the Deerfield Loan, in the aggregate principal amount of $25.0 million and (ii) warrants to purchase up to 8,333 shares of our common stock at an exercise price of $2,360.40 per share held by Deerfield were cancelled in consideration for (i) a cash payment in the aggregate amount of $2.5 million, (ii) 23,703 shares of common stock, representing 2% of fully-diluted shares outstanding (as defined in the Exchange and Termination Agreement) on the closing date, and (iii) the right to receive certain milestone payments based on achievement of specified AEROSURF development and commercial milestones, which, if achieved, could potentially total up to $15.0 million. In addition, a related security agreement, pursuant to which Deerfield held a security interest in substantially all of our assets, was terminated. We established a $15.0 million long-term liability for the contingent milestone payments potentially due to Deerfield under the Exchange and Termination Agreement (*see*, Note 4 – Accounting Policies and Recent Accounting Pronouncements). The liability has been recorded at the full value of the contingent milestones and will continue to be carried at full value until the milestones are achieved and paid or the milestones are not achieved and the liability is written off as a gain on debt restructuring.

As of December 31, 2021 and 2020, the restructured debt liability balance was $15.0 million.

CRITICAL ACCOUNTING POLICIES AND ESTIMATES

The preceding discussion and analysis of financial condition and results of operations are based upon our Consolidated Financial Statements, which have been prepared in conformity with U.S. generally accepted accounting principles, or GAAP. Preparing financial statements requires us to make estimates and assumptions that affect the reported amounts of assets, liabilities, revenues and expenses. Estimates are based on our historical operations, our future business plans and projected financial results, the terms of existing contracts, our observance of trends in the industry, and information available from other outside sources, as appropriate. These estimates and assumptions are affected by the application of our accounting policies. Critical accounting policies and practices are both important to the portrayal of a company's financial condition and results of operations, and require management's most difficult, subjective or complex judgments, often as a result of the need to make estimates about the effects of matters that are inherently uncertain. Actual results could differ from such estimates due to changes in economic factors or other conditions that are outside the control of management. A summary of our significant accounting policies is described in Note 4 of the Audited Consolidated Financial Statements contained in this Annual Report on Form 10-K. Of those policies, we believe that the following accounting policy is critical to aid our stockholders in fully understanding and evaluating our reported financial results.

Intangible Assets and Goodwill

We record acquired identified intangibles, which includes intangible assets (such as goodwill and other intangibles), based on estimated fair value. The acquired IPR&D assets are considered indefinite-lived intangible assets until completion or abandonment of the associated research and development efforts. IPR&D is not amortized but reviewed for impairment at least annually, or when events or changes in the business environment indicate that the carrying value may be impaired.

When testing our goodwill and indefinite-lived intangible assets for impairment, we can elect to perform a qualitative assessment to determine if it is more likely than not that the fair values of our reporting unit and indefinite-lived intangible assets are less than their respective carrying values. Such qualitative factors can include, among others, industry and market conditions, overall financial performance, and relevant entity-specific events. If we conclude based on our qualitative assessment that it is more likely than not that the fair value of our reporting unit or indefinite-lived intangible assets are less than their respective carrying values, we perform a quantitative assessment. When conducting our annual impairment test of goodwill and indefinite-lived intangible assets as of December 1, 2021, we elected to perform a quantitative assessment.

When performing the quantitative impairment assessment for our indefinite-lived IPR&D intangible assets, we estimate the fair values of the assets using the multi-period excess earnings method, or MPEEM. MPEEM is a variation of the income approach which estimates the fair value of an intangible asset based on the present value of the incremental after-tax cash flows attributable to the intangible asset. Significant factors considered in the calculation of IPR&D intangible assets include the risks inherent in the development process, including the likelihood of achieving commercial success and the cost and related time to complete the remaining development. Future cash flows for each project were estimated based on forecasted revenue and costs, taking into account the expected product life cycles, market penetration, and growth rates. Other significant estimates and assumptions inherent in this approach include (i) the amount and timing of the projected net cash flows associated with the IPR&D assets, (ii) the discount rate, which seeks to reflect the various risks inherent in the projected cash flows; and (iii) the tax rate, which considers geographic diversity of the projected cash flows. While we use the best available information to prepare our cash flows and discount rate assumptions, actual future cash flows could differ significantly based on the commercial success of the related drug candidates and market conditions which could result in future impairment charges related to our indefinite-lived intangible asset balances.

During the second quarter of 2021, we concluded an initial process to test the industry's interest in investing in our rostafuroxin drug candidate and were not able to secure a licensing transaction or other strategic opportunity at that time. Based on feedback received from potential licensing partners, we have determined that there is a need for an additional phase 2 clinical trial to demonstrate efficacy in non-Caucasian patients in treatment resistant hypertension. Due to these developments, and in connection with the preparation of the interim unaudited condensed consolidated financial statements as of and for the period ending June 30, 2021, we determined that the fair value of the IPR&D related to our rostafuroxin drug candidate was more likely than not less than its carrying value. As a result, we performed the required quantitative impairment assessment of the related intangible asset. We estimated the fair value of the asset using MPEEM and determined that the fair value as of June 30, 2021 was approximately $17.0 million. We then compared this fair value to the carrying value of approximately $54.8 million and recorded a loss on impairment of intangible assets of $37.8 million during the second quarter of 2021.

As part of our annual quantitative impairment assessment of indefinite-lived IPR&D intangible assets, we reassessed certain of the assumptions related to our rostafuroxin drug candidate due to the current macroeconomic conditions which have made it harder to secure the funding needed to conduct the additional phase 2 clinical trial and have therefore delayed our intended development of rostafuroxin. As a result, we concluded that the fair value of the IPR&D related to our rostafuroxin drug candidate was again less than its carrying value. We estimated the fair value of the asset using MPEEM and determined that the fair value as of December 1, 2021 was approximately $9.7 million. We then compared this fair value to the carrying value of approximately $17.0 million, and recorded an additional loss on impairment of intangible assets of $7.2 million in the fourth quarter of 2021. When combined with the loss on impairment of intangible assets recorded during the second quarter, we recorded a loss on impairment of intangible assets totaling $45.0 million within operating expenses in our consolidated statements of operations during the year ended December 31, 2021. No events or changes in the business environment occurred during 2021 that would indicate that the fair value of the IPR&D related to our istaroxime drug candidate was impaired.

Goodwill represents the excess of the purchase price over the fair value of assets acquired and liabilities assumed in a business combination and is not amortized. It is reviewed for impairment at least annually or when events or changes in the business environment indicate that its carrying value may be impaired. Our company consists of one reporting unit. In order to perform the quantitative goodwill impairment test, we compare the estimated fair value of our reporting unit to its carrying value. If the fair value exceeds the carrying value, no further evaluation is required, and no impairment exists. If the carrying value exceeds the fair value, the difference between the carrying value and the fair value is recorded as an impairment loss, the amount of which may not exceed the total amount of goodwill. When performing our annual goodwill impairment assessment as of December 1, 2021, we estimated the fair value of our reporting unit based upon the quoted market price and related market capitalization of our common stock, adjusted for an estimated control premium. Based on the quantitative test performed, we determined that the fair value of our reporting unit exceeded its carrying value and no impairment exists.

The following table represents identifiable intangible assets and goodwill as of December 1, 2021 and 2020:

(in thousands)	December 31, 2021	December 31, 2020
Istaroxime drug candidate	$ 22,340	$ 22,340
Rostafuroxin drug candidate	9,730	54,750
Intangible assets	32,070	77,090
Goodwill	$ 15,682	$ 15,682

Accrued Research and Development Expenses

As part of the process of preparing our financial statements, we are required to estimate our accrued expenses. This process involves reviewing quotations and contracts, identifying services that have been performed on our behalf and estimating the level of service performed and the associated cost incurred for the service when we have not yet been invoiced or otherwise notified of the actual cost. The majority of our service providers invoice us monthly in arrears for services performed or when contractual milestones are met. We make estimates of our accrued expenses as of each balance sheet date in our financial statements based on facts and circumstances known to us at that time. We periodically confirm the accuracy of our estimates with the service providers and make adjustments if necessary. The significant estimates in our accrued research and development expenses are related to expenses incurred with respect to CROs, CMOs, clinical trial sites, and other vendors supporting our research and development and manufacturing activities.

We base our expenses related to CROs, CMOs and clinical trial sites on our estimates of services received and efforts expended under quotations and contracts with those vendors that conduct research and development and manufacturing activities on our behalf. The financial terms of these agreements are negotiated, vary from contract to contract and may result in uneven payment flows. At times, payments made to our vendors may exceed the level of services provided and result in a prepayment of the applicable research and development or manufacturing expense. In accruing service fees, we estimate the time period over which services will be performed and the level of effort to be expended in each period. If the actual timing of the performance of services or the level of effort varies from our estimate, we adjust the accrual or prepaid expense accordingly. Although we do not expect our estimates to be materially different from amounts actually incurred, our understanding of the status and timing of services performed relative to the actual status and timing of services performed may vary and could result in us reporting amounts that are too high or too low in any particular period. There have been no material changes in estimates for the periods presented.

ITEM 7A. QUANTITATIVE AND QUALITATIVE DISCLOSURES ABOUT MARKET RISK.

Not applicable.

ITEM 8. FINANCIAL STATEMENTS AND SUPPLEMENTARY DATA.

The information required by this Item is set forth in the financial statements and notes thereto beginning at page F-1 of this Annual Report on Form 10-K.

ITEM 9. CHANGES IN AND DISAGREEMENTS WITH ACCOUNTANTS ON ACCOUNTING AND FINANCIAL DISCLOSURE.

None.

ITEM 9A. CONTROLS AND PROCEDURES.

(a) Evaluation of Disclosure Controls and Procedures

Our management, including our President and Chief Executive Officer (principal executive officer) and our Senior Vice President and Chief Financial Officer and Treasurer (principal financial and accounting officer), do not expect that our disclosure controls or our internal control over financial reporting will prevent all error and all fraud. Because of the inherent limitations in all control systems, no evaluation of controls can provide absolute assurance that all control issues and instances of fraud, if any, have been detected. These inherent limitations include the realities that judgments in decision-making can be faulty and that breakdowns can occur because of simple error or mistake. Controls can also be circumvented by the individual acts of some persons, by collusion of two or more people, or by management override of the controls. The design of any system of controls is based in part on certain assumptions about the likelihood of future events, and there can be no assurance that any design will succeed in achieving its stated goals under all potential future conditions. Over time, controls may become inadequate because of changes in conditions or deterioration in the degree of compliance with policies or procedures. Because of the inherent limitations in a cost-effective control system, misstatements due to error or fraud may occur and not be detected. In designing and evaluating the disclosure controls and procedures, our management recognized that any controls and procedures, no matter how well designed and operated, can provide only reasonable assurance of achieving the desired control objectives and our management necessarily was required to apply its judgment in evaluating the cost-benefit relationship of possible controls and procedures.

Our President and Chief Executive Officer and our Senior Vice President and Chief Financial Officer and Treasurer have evaluated the effectiveness of the design and operation of our disclosure controls and procedures (as defined in Rule 13a-15(e) and Rule 15d-15(e) of the Exchange Act) as of the end of the period covered by this Annual Report on Form 10-K. Based on this evaluation, our President and Chief Executive Officer and our Senior Vice President and Chief Financial Officer and Treasurer concluded that, as of the end of the period covered by this report, our disclosure controls and procedures were effective to ensure that information required to be disclosed by us in the reports that we file or submit under the Exchange Act is accumulated and communicated to our management, including our President and Chief Executive Officer and our Senior Vice President and Chief Financial Officer and Treasurer, to allow for timely decisions regarding required disclosures, and recorded, processed, summarized and reported within the time periods specified in the SEC's rules and forms.

(b) Management's Report on Internal Control over Financial Reporting

Our management is responsible for establishing and maintaining adequate internal control over financial reporting, as such term is defined in Rule 13a-15(f) promulgated under the Exchange Act. Our internal control system is designed to provide reasonable assurance to our management and Board of Directors regarding the preparation and fair presentation of published financial statements. All internal control systems, no matter how well designed, have inherent limitations. Therefore, even those systems determined to be effective can provide only reasonable assurance with respect to financial statement preparation and presentation.

Under the supervision and with the participation of our management, including our President and Chief Executive Officer and our Senior Vice President and Chief Financial Officer and Treasurer, our management conducted an evaluation of the effectiveness of our internal control over financial reporting as of December 31, 2021. In making this assessment, our management used the criteria set forth by the Committee of Sponsoring Organizations of the Treadway Commission, or COSO, in Internal Control-Integrated 2013 Framework. Based on our assessment, our management believes that our internal control over financial reporting is effective based on those criteria, as of December 31, 2021.

This Annual Report on Form 10-K does not include an attestation report of our registered public accounting firm regarding internal control over financial reporting. Management's report was not subject to attestation by our registered public accounting firm pursuant to rules of the Securities and Exchange Commission that permit us to provide only management's report in this Annual Report on Form 10-K.

(c) Changes in Internal Controls

There were no changes in our internal control over financial reporting identified in connection with the evaluation described above that occurred during the quarter ended December 31, 2021 that has materially affected, or is reasonably likely to materially affect, our internal control over financial reporting.

ITEM 9B. OTHER INFORMATION.

None.

ITEM 9C. DISCLOSURE REGARDING FOREIGN JURISDICTIONS THAT PREVENT INSPECTIONS.

Not applicable.

PART III

ITEM 10. DIRECTORS, EXECUTIVE OFFICERS AND CORPORATE GOVERNANCE

The information required by this Item is incorporated herein by reference from our proxy statement on Schedule 14A, or the Proxy Statement, for our 2022 Annual Meeting of Stockholders.

ITEM 11. EXECUTIVE COMPENSATION

The information required by this Item is incorporated herein by reference from our Proxy Statement for our 2022 Annual Meeting of Stockholders.

ITEM 12. SECURITY OWNERSHIP OF CERTAIN BENEFICIAL OWNERS AND MANAGEMENT AND RELATED STOCKHOLDER MATTERS

The information required by this Item is incorporated herein by reference from our Proxy Statement for our 2022 Annual Meeting of Stockholders.

ITEM 13. CERTAIN RELATIONSHIPS AND RELATED TRANSACTIONS, AND DIRECTOR INDEPENDENCE

The information required by this Item is incorporated herein by reference from our Proxy Statement for our 2022 Annual Meeting of Stockholders.

ITEM 14. PRINCIPAL ACCOUNTANT FEES AND SERVICES

The information required by this Item is incorporated herein by reference from our Proxy Statement for our 2022 Annual Meeting of Stockholders.

PART IV

ITEM 15. EXHIBITS AND FINANCIAL STATEMENT SCHEDULES.

(a) Financial Statements.

The consolidated financial statements required to be filed in this Annual Report on Form 10-K are listed on the Index to Consolidated Financial Statements on page F-1 hereof.

(b) Exhibits.

The following exhibits are included with this Annual Report on Form 10-K.

Exhibit No.	Description
3.1	Amended and Restated Certificate of Incorporation (incorporated by reference to Exhibit 3.1 to Windtree's Annual Report on Form 10-K, as filed with the SEC on April 17, 2018).
3.2	Certificate of Amendment to the Amended and Restated Certificate of Incorporation (incorporated by reference to Exhibit 3.1 to Windtree's Current Report on Form 8-K, as filed with the SEC on April 29, 2020).
3.3	Amended and Restated By-Laws (incorporated by reference to Exhibit 3.2 to Windtree's Form 8-K filed on April 18, 2016).
4.1	Form of Warrant dated October 10, 2014 (incorporated by reference to Exhibit 4.11 to Windtree's Quarterly Report on Form 10-Q, as filed with the SEC on November 7, 2014).
4.2	Form of Series A Warrant dated July 22, 2015 (incorporated by reference to Exhibit 4.1 to Windtree's Current Report on Form 8-K, as filed with the SEC on July 17, 2015).

4.3	Form of Series B Warrant dated July 22, 2015 (incorporated by reference to Exhibit 4.3 to Windtree's Current Report on Form 8-K, as filed with the SEC on July 17, 2015).
4.4	Form of Series A-1 Warrant dated February 13, 2017 (incorporated by reference to Exhibit 4.1 to Windtree's Current Report on Form 8-K, as filed with the SEC on February 15, 2017).
4.5	Form of Series C Warrant dated April 4, 2018 (incorporated by reference to Exhibit 4.1 to Windtree's Current Report on Form 8-K, as filed with the SEC on April 4, 2018).
4.6	Form of Series D Warrant dated July 2, 2018 (incorporated by reference to Exhibit 4.1 to Windtree's Current Report on Form 8-K, as filed with the SEC on July 6, 2018).
4.7	Form of Series E Warrant dated December 11, 2018 (incorporated by reference to Exhibit 4.7 to Windtree's Annual Report on Form 10-K, as filed with the SEC on April 16, 2019).
4.8	Form of Series F Warrant dated December 24, 2018 (incorporated by reference to Exhibit 4.2 to Windtree's Current Report on Form 8-K, as filed with the SEC on December 21, 2018).
4.9	Form of Series G Warrant dated December 24, 2018 (incorporated by reference to Exhibit 4.3 to Windtree's Current Report on Form 8-K, as filed with the SEC on December 21, 2018).
4.10	Form of Series H Warrant dated February 14, 2019 (incorporated by reference to Exhibit 4.1 to Windtree's Current Report on Form 8-K, as filed with the SEC on December 21, 2018).
4.11	Form of Series I Warrant dated December 6, 2019 (incorporated by reference to Exhibit 4.1 to Windtree's Current Report on Form 8-K, as filed with the SEC on December 9, 2019).
4.12	Form of Series F Warrant Amendment No. 1 dated April 24, 2020 (incorporated by reference to Exhibit 4.1 to Windtree's Current Report on Form 8-K, as filed with the SEC on April 29, 2020).
4.13	Form of Series I Warrant Amendment dated May 6, 2020, to the Series I Warrant dated December 6, 2019 (incorporated by reference to Exhibit 4.1 to Windtree's Current Report on Form 8-K, as filed with the SEC on May 7, 2020).
4.14	Form of Warrant issued in the Company's May 2020 underwritten public offering of securities (incorporated by reference to Exhibit 4.1 to Windtree's Current Report on Form 8-K, as filed with the SEC on May 22, 2020).
4.15	Form of Warrant issued in the Company's March 2021 underwritten public offering of securities (incorporated by reference to Exhibit 4.1 to Windtree's Current Report on Form 8-K, as filed with the SEC on March 24, 2021.
4.16	Description of Securities. (incorporated by reference to Exhibit 4.16 to Windtree's Annual Report on Form 10-K, as filed with the SEC on March 29, 2021).
10.1†	Sublicense Agreement dated October 28, 1996 between Johnson & Johnson, Ortho Pharmaceutical Corporation and Acute Therapeutics, Inc. (incorporated by reference to Exhibit 10.6 to Windtree's Registration Statement on Form SB-2/A, as filed with the SEC on April 18, 1997 (Commission File Number 333-19375)).
10.2†	Amended and Restated License Agreement dated March 28, 2008, between Windtree and Philip Morris USA Inc. (incorporated by reference to Exhibit 10.4 to Windtree's Quarterly Report on Form 10-Q for the quarter ended March 31, 2008, as filed with the SEC on May 9, 2008).
10.3†	License Agreement dated March 28, 2008, between Windtree and Philip Morris Products S.A. (incorporated by reference to Exhibit 10.5 to Windtree's Quarterly Report on Form 10-Q for the quarter ended March 31, 2008, as filed with the SEC on May 9, 2008).
10.4††	Amended and Restated Sublicense and Collaboration Agreement dated December 3, 2004, by and between Discovery Laboratories, Inc. (predecessor-in-interest to Windtree) and Laboratorios del Dr. Esteve, S.A. (incorporated by reference to Exhibit 10.3 to Windtree's Quarterly Report on Form 10-Q for the quarter ended September 30, 2020, as filed with the SEC on November 16, 2020).
10.5††	Amended and Restated Supply Agreement dated December 3, 2004, by and between Discovery Laboratories, Inc. (predecessor-in-interest to Windtree) and Laboratorios del Dr. Esteve, S.A. (incorporated by reference to Exhibit 10.2 to Windtree's Quarterly Report on Form 10-Q for the quarter ended September 30, 2020, as filed with the SEC on November 16, 2020).
10.6†	License, Development and Commercialization Agreement dated June 12, 2017, between Windtree and Lee's Pharmaceutical (HK) Ltd. (incorporated by reference to Exhibit 10.1 to Windtree's Quarterly Report on Form 10-Q for the quarter ended June 30, 2017, as filed with the SEC on August 21, 2017).
10.7†	Amendment No. 1 dated August 14, 2017 to the License Development and Commercialization Agreement between Windtree and Lee's Pharmaceutical (HK) Ltd. dated June 12, 2017 (incorporated by reference to Exhibit 10.1 to Windtree's Quarterly Report on Form 10-Q for the quarter ended September 30, 2017, as filed with the SEC on November 14, 2017).

10.8#	Windtree's 2011 Long-Term Incentive Plan, as amended (incorporated by reference to Exhibit 10.1 to Windtree's Current Report on Form 8-K, as filed with the SEC on December 31, 2018).
10.9#	Windtree's 2020 Equity Incentive Plan (incorporated by reference to Exhibit 10.1 to Windtree's Current Report on Form 8-K, as filed with the SEC on December 31, 2020).
10.10#	Form of Restricted Stock Unit Grant for Employees under Windtree's 2020 Equity Incentive Plan (incorporated by reference to Exhibit 4.5 To Windtree's Registration Statement on Form S-8, as filed with the SEC on February 12, 2021).
10.11#	Form of Stock Option Grant for Employees under Windtree's 2020 Equity Incentive Plan (incorporated by reference to Exhibit 4.6 To Windtree's Registration Statement on Form S-8, as filed with the SEC on February 12, 2021).
10.12#	Form of Inducement Award Agreement (incorporated by reference to Exhibit 4.4 to Windtree's Registration Statement on Form S-8 (File No. 333-253067), as filed with the SEC on February 12, 2021)
10.13#	Form of Employee Option Agreement under Windtree's 2011 Long-Term Incentive Plan (incorporated by reference to Exhibit 10.2 to Windtree's Quarterly Report on Form 10-Q for the quarter ended March 31, 2012, as filed with the SEC on May 15, 2012).
10.14#	Form of Non-Employee Director Option Agreement under Windtree's 2011 Long-Term Incentive Plan (incorporated by reference to Exhibit 10.10 to Windtree's Form 10-K, as filed with the SEC on April 3, 2020).
10.15#	Form of Restricted Stock Unit Award Agreement for Non-Employee Directors under Windtree's 2011 Long-Term Incentive Plan (incorporated by reference to Exhibit 10.11 to Windtree's Annual Report on Form 10-K for the year ended December 31, 2014, as filed with the SEC on March 16, 2015).
10.16#	Form of Restricted Stock Unit Award Agreement for Employees under Windtree's 2011 Long-Term Incentive Plan (incorporated by reference to Exhibit 10.14 to Windtree's Annual Report on Form 10-K for the year ended December 31, 2017, as filed with the SEC on April 17, 2018).
10.17#	Employment Agreement dated February 1, 2016, between Windtree and Craig Fraser (incorporated by reference to Exhibit 10.1 to Windtree's Current Report on Form 8-K, as filed with the SEC on February 3, 2016).
10.18#	Inducement Stock Option Award Agreement dated February 1, 2016, between Windtree and Craig Fraser (incorporated by reference to Exhibit 10.3 to Windtree's Current Report on Form 8-K, as filed with the SEC on February 3, 2016).
10.19#	Amendment dated March 13, 2018, to Employment Agreement dated February 1, 2016, between Windtree and Craig Fraser (incorporated by reference to Exhibit 10.1 to Windtree's Current Report on Form 8-K, as filed with the SEC on March 16, 2018).
10.20#	Employment Agreement dated December 19, 2014, between Windtree and Steven G. Simonson, M.D. (incorporated by reference to Exhibit 10.4 to Windtree's Quarterly Report on Form 10-Q, as filed with the SEC on May 11, 2015).
10.21#	Amendment dated December 29, 2014 to Employment Agreement dated December 19, 2014, effective as of April 1, 2015, between Windtree and Steven G. Simonson, M.D. (incorporated by reference to Exhibit 10.5 to Windtree's Quarterly Report on Form 10-Q, as filed with the SEC on May 11, 2015).
10.22#	Amendment dated March 13, 2018, to Employment Agreement dated December 19, 2014 between Windtree and Steven G. Simonson, M.D. (incorporated by reference to Exhibit 10.3 to Windtree's Current Report on Form 8-K, as filed with the SEC on March 16, 2018).
10.23#	At The Market Offering Agreement, dated as of September 17, 2020, by and between Windtree Therapeutics, Inc. and Ladenburg Thalmann & Co. Inc. (incorporated by reference to Exhibit 1.2 to the Windtree's Registration Statement on Form S-3, as filed with the SEC on September 17, 2020).
10.24#	Form of Indemnification Agreement between Windtree and certain named executive officers and directors (incorporated by reference to Exhibit 10.4 to Windtree's Current Report on Form 8-K, as filed with the SEC on February 3, 2016).
10.25	Form of Indemnification Agreement between Windtree and certain named directors (incorporated by reference to Exhibit 10.23 to Windtree's Annual Report on Form 10-K, as filed with the SEC on April 16, 2019).
10.26	Lease Agreement dated May 26, 2004, and First Amendment to Lease Agreement, dated April 2, 2007, between TR Stone Manor Corp. and Windtree (incorporated by reference to Exhibits 10.1 and 10.2 to Windtree's Current Report on Form 8-K, as filed with the SEC on April 6, 2007).
10.27	Second Amendment to Lease Agreement dated January 3, 2013 between TR Stone Manor Corp. and Windtree (incorporated by reference to Exhibit 10.1 to Windtree's Current Report on Form 8-K, as filed with the SEC on January 8, 2013).
10.28	Fourth Amendment to Lease Agreement dated April 29, 2016, between PH Stone Manor LP and Windtree (incorporated by reference to Exhibit 10.1 to Windtree's Current Report on Form 8-K, as filed with the SEC on May 31, 2016).

10.29	Fifth Amendment to Lease Agreement dated February 23, 2018, between PH Stone Manor LP and Windtree (incorporated by reference to Exhibit 10.1 to Windtree's Current Report on Form 8-K, as filed with the SEC on March 1, 2018).
10.30†	Master Services Agreement dated October 24, 2013 between Windtree and DSM Pharmaceuticals, Inc. (now known as Patheon Manufacturing Services LLC) (incorporated by reference to Exhibit 10.3 to Windtree's Quarterly Report on Form 10-Q, as filed with the SEC on November 12, 2013).
10.31†	Supply Agreement dated December 22, 2010 between Corden Pharma (formerly Genzyme Pharmaceuticals LLC, now known as Corden Pharma) and Windtree (incorporated by reference to Exhibit 10.1 to Windtree's Current Report on Form 8-K, as filed with the SEC on December 29, 2010).
10.32	Exchange and Termination Agreement dated October 27, 2017, between Windtree and Deerfield (incorporated by reference to Exhibit 10.2 to Windtree's Current Report on Form 8-K, as filed with the SEC on November 1, 2017).
10.33	Registration Rights Agreement dated October 27, 2017, between Windtree and LPH Investments Limited (incorporated by reference to Exhibit 99.1 to Windtree's Current Report on Form 8-K, as filed with the SEC on November 1, 2017).
10.34	Registration Rights Agreement dated March 30, 2018, between Windtree and LPH II Investments Limited (incorporated by reference to Exhibit 10.2 to Windtree's Current Report on Form 8-K, as filed with the SEC on April 4, 2018).
10.35††	Collaboration Agreement dated as of October 14, 2014, by and between Battelle Memorial Institute and Discovery Laboratories, Inc. (predecessor-in-interest to Windtree) (incorporated by reference to Exhibit 10.1 to Windtree's Quarterly Report on Form 10-Q for the quarter ended September 30, 2020, as filed with the SEC on November 16, 2020).
10.36	Payment Restructuring Agreement effective December 7, 2018, between Windtree and Battelle Memorial Institute (incorporated by reference to Exhibit 10.1 to Windtree's Current Report on Form 8-K, as filed with the SEC on December 7, 2018).
10.37	Amendment No. 1 dated March 30, 2020 to Payment Restructuring Agreement, effective December 7, 2018, between Windtree and Lee's Pharmaceutical (HK) LTD (incorporated by reference to Exhibit 10.48 to Windtree's Registration Statement on Form S-1/A (File No. 333-236085), as filed with the SEC on May 6, 2020).
10.38	Loan Agreement dated October 25, 2018, between CVie Therapeutics, Lee's Pharmaceutical Holdings Limited, and O-Bank Co., Ltd. (incorporated by reference to Exhibit 10.34 to Windtree's Annual Report on Form 10-K, as filed with the SEC on April 16, 2019).
10.39	Shareholder Loan Agreement dated April 24, 2018, between Lee's Pharmaceutical International Limited and CVie Therapeutics (incorporated by reference to Exhibit 10.35 to Windtree's Annual Report on Form 10-K, as filed with the SEC on April 16, 2019).
10.40	Shareholder Loan Agreement dated September 20, 2018, between Lee's Pharmaceutical International Limited and CVie Therapeutics (incorporated by reference to Exhibit 10.36 to Windtree's Annual Report on Form 10-K, as filed with the SEC on April 16, 2019).
10.41	Shareholder Loan Agreement dated October 26, 2018, between Lee's Pharmaceutical International Limited and CVie Therapeutics (incorporated by reference to Exhibit 10.37 to Windtree's Annual Report on Form 10-K, as filed with the SEC on April 16, 2019).
10.42	Shareholder Loan Agreement dated November 16, 2018, between Lee's Pharmaceutical International Limited and CVie Therapeutics (incorporated by reference to Exhibit 10.38 to Windtree's Annual Report on Form 10-K, as filed with the SEC on April 16, 2019).
10.43	Merger Agreement dated December 21, 2018, between Windtree, WT Acquisition Corp., and CVie Investments Limited (incorporated by reference to Exhibit 10.1 to Windtree's Current Report on Form 8-K, as filed with the SEC on December 21, 2018).
10.44	Indemnification Letter Agreement dated December 21, 2018, between Windtree and Lee's Pharmaceutical Holdings Limited (incorporated by reference to Exhibit 10.2 to Windtree's Current Report on Form 8-K, as filed with the SEC on December 21, 2018).
10.45	Securities Purchase Agreement dated December 21, 2018 between Windtree and certain purchasers party thereto (incorporated by reference to Exhibit 10.3 to Windtree's Current Report on Form 8-K, as filed with the SEC on December 21, 2018).
10.46	Registration Rights Agreement dated December 21, 2018 between Windtree and certain purchasers party thereto (incorporated by reference to Exhibit 10.4 to Windtree's Current Report on Form 8-K, as filed with the SEC on December 21, 2018).
10.47	Loan Agreement dated October 24, 2019 between Windtree and LPH II Investments Ltd. (incorporated by reference to Exhibit 10.1 to Windtree's Current Report on Form 8-K, as filed with the SEC on October 28, 2019).

10.48	Form of Securities Purchase Agreement dated December 6, 2019 by and among Windtree and the purchasers party thereto (incorporated by reference to Exhibit 10.1 to Windtree's Current Report on Form 8-K, as filed with the SEC on December 9, 2019).
10.49	Form of Registration Rights Agreement dated December 6, 2019 by and among Windtree and the purchasers party thereto (incorporated by reference to Exhibit 10.2 to Windtree's Current Report on Form 8-K, as filed with the SEC on December 9, 2019).
10.50#	Employment Agreement dated March 1, 2020, between Windtree and Eric Curtis (incorporated by reference to Exhibit 10.46 to Windtree's Form 10-K, as filed with the SEC on April 3, 2020).
10.51	Amendment to No. 1 dated February 20, 2020 to the Securities Purchase Agreement dated December 6, 2019 by and among Windtree and the purchasers party thereto (incorporated by reference to Exhibit 10.47 to Windtree's Form 10-K, as filed with the SEC on April 3, 2020).
10.52	Project Financing Agreement, dated August 12, 2020, by and between Windtree and Lee's Pharmaceutical (HK) Ltd. (incorporated by reference to Exhibit 10.4 to Windtree's Quarterly Report on Form 10-Q, as filed with the SEC on November 16, 2020).
10.53#	Employment Agreement by and between Windtree and John Hamill, dated as of July 20, 2020 (incorporated by reference to Exhibit 10.1 to Windtree's Current Report on Form 8-K, as filed with the SEC on July 23, 2020).
10.54#*	Employment Agreement by and between Windtree and Diane Carman, dated as of July 1, 2021.
21.1	Subsidiaries of Windtree (incorporated by reference to Exhibit 21.1 to Windtree's Annual Report on Form 10-K, as filed with the SEC on April 16, 2019).
23.1*	Consent of Ernst & Young LLP, independent registered public accounting firm.
31.1*	Certification of the Chief Executive Officer, as required by Section 302 of the Sarbanes-Oxley Act of 2002.
31.2*	Certification of the Chief Financial Officer, as required by Section 302 of the Sarbanes-Oxley Act of 2002.
32.1*	Certifications of the Chief Executive Officer and Chief Financial Officer as required by 18 U.S.C. 1350.
101.INS*	Inline XBRL Instance Document (the Instance Document does not appear in the Interactive Data File because its XBRL tags are embedded within the Inline XBRL document) (1).
101.SCH*	Inline XBRL Taxonomy Extension Schema Document (1).
101.CAL*	Inline XBRL Taxonomy Extension Calculation Linkbase Document (1).
101.DEF*	Inline XBRL Taxonomy Extension Definition Linkbase Document (1).
101.LAB*	Inline XBRL Taxonomy Extension Label Linkbase Document (1).
101.PRE*	Inline XBRL Taxonomy Extension Presentation Linkbase Document (1).
104	Cover Page Interactive Data File (formatted as Inline XBRL and combined in Exhibit 101.1)

* Filed herewith.
# Compensation Related Contract.
† Confidential treatment received for certain portions of this exhibit.
†† Certain confidential portions have been omitted from this exhibit pursuant to Item 601(b)(10)(iv) of Regulation S-K.
(1) These Interactive Data Files shall not be deemed filed for purposes of Section 11 or 12 of the Securities Act of 1933, as amended, or Section 18 of the Securities Exchange Act of 1934, as amended, or otherwise subject to liability under those sections.

SIGNATURES

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

WINDTREE THERAPEUTICS, INC.

Date: March 31, 2022

By: /s/ Craig E. Fraser
Craig E. Fraser
Director, President, and Chief Executive Officer

Pursuant to the requirements of the Securities Exchange Act of 1934, this report has been signed below by the following persons on behalf of the registrant and in the capacities and on the dates indicated.

Signature	Title	Date
/s/ Craig E. Fraser Craig E. Fraser	Director, President, and Chief Executive Officer (Principal Executive Officer)	March 31, 2022
/s/ John P. Hamill John P. Hamill	Senior Vice President and Chief Financial Officer and Treasurer (Principal Financial and Accounting Officer)	March 31, 2022
/s/ James Huang James Huang	Director (Chairman of the Board)	March 31, 2022
/s/ Daniel E. Geffken Daniel E. Geffken	Director	March 31, 2022
/s/ Evan Loh, M.D. Evan Loh, M.D.	Director	March 31, 2022
/s/ Robert Scott, M.D. Robert Scott, M.D.	Director	March 31, 2022
/s/ Leslie J. Williams Leslie J. Williams	Director	March 31, 2022

WINDTREE THERAPEUTICS, INC. AND SUBSIDIARIES

Contents

WINDTREE THERAPEUTICS, INC. AND SUBSIDIARIES

Report of Independent Registered Public Accounting Firm

To the Stockholders and the Board of Directors of Windtree Therapeutics, Inc.

Opinion on the Financial Statements

We have audited the accompanying consolidated balance sheets of Windtree Therapeutics, Inc. and subsidiaries (the Company) as of December 31, 2021 and 2020, the related consolidated statements of operations**,** changes in stockholders' equity and cash flows for the years then ended, and the related notes (collectively referred to as the "consolidated financial statements"). In our opinion, the consolidated financial statements present fairly, in all material respects, the financial position of the Company at December 31, 2021 and 2020, and the results of its operations and its cash flows for the years then ended, in conformity with U.S. generally accepted accounting principles.

The Company's Ability to Continue as a Going Concern

The accompanying consolidated financial statements have been prepared assuming that the Company will continue as a going concern. As discussed in Note 3 to the consolidated financial statements, the Company has suffered recurring losses from operations, expects to incur losses for the foreseeable future, and has stated that substantial doubt exists about the Company's ability to continue as a going concern. Management's evaluation of the events and conditions and management's plans regarding these matters are also described in Note 3. The consolidated financial statements do not include any adjustments that might result from the outcome of this uncertainty.

Basis for Opinion

These financial statements are the responsibility of the Company's management. Our responsibility is to express an opinion on the Company's financial statements based on our audits. We are a public accounting firm registered with the Public Company Accounting Oversight Board (United States) (PCAOB) and are required to be independent with respect to the Company in accordance with the U.S. federal securities laws and the applicable rules and regulations of the Securities and Exchange Commission and the PCAOB.

We conducted our audits in accordance with the standards of the PCAOB. Those standards require that we plan and perform the audit to obtain reasonable assurance about whether the financial statements are free of material misstatement, whether due to error or fraud. The Company is not required to have, nor were we engaged to perform, an audit of its internal control over financial reporting. As part of our audits we are required to obtain an understanding of internal control over financial reporting but not for the purpose of expressing an opinion on the effectiveness of the Company's internal control over financial reporting. Accordingly, we express no such opinion.

Our audits included performing procedures to assess the risks of material misstatement of the financial statements, whether due to error or fraud, and performing procedures that respond to those risks. Such procedures included examining, on a test basis, evidence regarding the amounts and disclosures in the financial statements. Our audits also included evaluating the accounting principles used and significant estimates made by management, as well as evaluating the overall presentation of the financial statements. We believe that our audits provide a reasonable basis for our opinion.

Critical Audit Matter

The critical audit matter communicated below is a matter arising from the current period audit of the financial statements that was communicated or required to be communicated to the audit committee and that: (1) relates to accounts or disclosures that are material to the financial statements and (2) involved our especially challenging, subjective or complex judgments. The communication of the critical audit matter does not alter in any way our opinion on the consolidated financial statements, taken as a whole, and we are not, by communicating the critical audit matter below, providing a separate opinion on the critical audit matter or on the account or disclosure to which it relates.

Fair value of indefinite-lived intangible assets

Description of the Matter

As reflected in the Company's consolidated financial statements, indefinite-lived intangible assets totaled $32.1 million and consisted of in-process research and development (IPR&D) at December 31, 2021. As discussed in Note 4 to the consolidated financial statements, IPR&D assets are tested by management for impairment at least annually, or when events or changes in the business environment indicate that the fair value of the IPR&D assets are more likely than not less than their carrying value. The Company recorded a loss on impairment of intangible assets of $45.0 million for the year-ended December 31, 2021. The interim and annual quantitative impairment tests require that management estimate the fair value of the IPR&D assets in order to determine if the asset is impaired.

Auditing the estimated fair value of the IPR&D assets was complex and involved a high degree of subjectivity due to the significant estimation uncertainty involved in determining the fair value of the IPR&D assets. In particular, the estimated fair value of the IPR&D assets was sensitive to significant assumptions such as the probability of achieving development and commercial success for the products, the size of the addressable patient population, the anticipated pricing for the products, the probability, timing and amount of any upfront or milestone payments from potential partnering agreements, the timing and amount of additional clinical trial costs to be incurred by the Company, and the discount rate.

Continued on next page

WINDTREE THERAPEUTICS, INC. AND SUBSIDIARIES

How We Addressed the Matter in Our Audit	To test the estimated fair value of the Company's IPR&D assets, we performed audit procedures that included, among others, testing the significant assumptions used to develop the estimate and evaluating the completeness and accuracy of the underlying data used by the Company in its analyses. For example, we compared the probability of achieving development and commercial success for the products to studies published in medical journals evaluating clinical advancement and approval rates for similar products. We compared the estimated size of the addressable patient population to an industry database that tracks healthcare information and we compared the anticipated pricing and upfront/milestone payment assumptions to publicly available data supporting transactions and products of a similar nature. We compared the anticipated future clinical trial costs to actual costs incurred by the Company for past comparable trials. We also involved internal valuation specialists to assist in our evaluation of the discount rate used by the Company.

/s/ Ernst & Young LLP
We have served as the Company's auditor since 2000.
Philadelphia, Pennsylvania
March 31, 2022

WINDTREE THERAPEUTICS, INC. AND SUBSIDIARIES
Consolidated Balance Sheets
(in thousands, except share and per share data)

	December 31, 2021	December 31, 2020
ASSETS		
Current Assets:		
Cash and cash equivalents	$ 22,348	$ 16,930
Prepaid expenses and other current assets	1,143	1,188
Total current assets	23,491	18,118
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	$ 74,789	$ 112,885
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	4,923	6,131
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	32,908	43,333
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	41,881	69,552
Total liabilities & stockholders' equity	$ 74,789	$ 112,885

See notes to consolidated financial statements

WINDTREE THERAPEUTICS, INC. AND SUBSIDIARIES
Consolidated Statements of Operations
(in thousands, except per share data)

	Year Ended December 31,	
	2021	**2020**
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 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	$ (67,636)	$ (32,566)
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

See notes to consolidated financial statements

WINDTREE THERAPEUTICS, INC. AND SUBSIDIARIES
Consolidated Statements of Changes in Stockholders' Equity
(in thousands)

	Common Stock				Treasury Stock		
	Shares	Amount	Additional Paid-in Capital	Accumulated Deficit	Shares	Amount	Total
Balance - December 31, 2019	**13,697**	**$ 14**	**$ 763,097**	**$ (685,122)**	**-**	**$ (3,054)**	**$ 74,935**
Net loss				(32,566)			(32,566)
Issuance of common stock and common stock warrants, net of issuance costs	3,172	3	20,243				20,246
Modification of warrants			1,112				1,112
Vesting of restricted stock units	35	-	-				-
Exercise of common stock warrants	18	-	141				141
Stock-based compensation expense			5,684				5,684
Balance - December 31, 2020	**16,922**	**$ 17**	**$ 790,277**	**$ (717,688)**	**-**	**$ (3,054)**	**$ 69,552**
Net loss				(67,636)			(67,636)
Issuance of common stock and common stock warrants, net of issuance costs	9,230	9	27,381				27,390
Issuance of common stock, ATM Program, net of issuance costs	2,117	2	4,841				4,843
Issuance of common stock warrants, equity consideration for service agreement			494				494
Stock-based compensation expense			7,238				7,238
Balance - December 31, 2021	**28,269**	**$ 28**	**$ 830,231**	**$ (785,324)**	**-**	**$ (3,054)**	**$ 41,881**

See notes to consolidated financial statements

WINDTREE THERAPEUTICS, INC. AND SUBSIDIARIES
Consolidated Statements of Cash Flows
(in thousands)

	Year Ended December 31,	
	2021	**2020**
Cash flows from operating activities:		
Net loss	$ (67,636)	$ (32,566)
Adjustments to reconcile net loss to net cash used in operating activities:		
Depreciation and amortization	192	168
Stock-based compensation	7,238	5,684
Non-cash expense related to warrant modifications	-	1,112
Non-cash lease expense	677	473
Non-cash expense related to equity consideration for a service agreement	494	-
Loss on impairment of intangible assets	45,020	-
Deferred income tax benefit	(9,987)	-
Unrealized loss on foreign exchange rate changes	396	1,142
Changes in assets and liabilities:		
Prepaid expenses and other current assets	1,365	1,147
Accounts payable	(468)	(547)
Collaboration and device development payable	-	(1,975)
Accrued expenses	(407)	585
Operating lease liabilities	(548)	(538)
Net cash used in operating activities	(23,664)	(25,315)
Cash flows from investing activities:		
Purchase of property and equipment	(279)	(291)
Net cash used in investing activities	(279)	(291)
Cash flows from financing activities:		
Proceeds from issuance of common stock and warrants, net of issuance costs	27,390	20,246
Proceeds from ATM Program, net of expenses	4,843	-
Proceeds from research and development funding arrangement	1,000	2,800
Proceeds from exercise of common stock warrants	-	141
Principal payments on loans payable	(3,872)	(3,229)
Proceeds from Paycheck Protection Program loan	-	547
Principal payments on Paycheck Protection Program loan	-	(547)
Net cash provided by financing activities	29,361	19,958
Net increase (decrease) in cash, cash equivalents, and restricted cash	5,418	(5,648)
Cash, cash equivalents, and restricted cash - beginning of year	17,084	22,732
Cash, cash equivalents, and restricted cash - end of year	$ 22,502	$ 17,084
Supplementary disclosure of non-cash activity:		
Operating lease liabilities arising from obtaining right-of-use assets	$ 2,141	$ 249
Prepayment of insurance through third-party financing	1,321	1,056

See notes to consolidated financial statements

WINDTREE THERAPEUTICS, INC. AND SUBSIDIARIES

Note 1 – The Company and Description of Business

We are a clinical-stage biopharmaceutical company focused on the development of novel therapeutics intended to address significant unmet medical needs in important acute care markets. Our development programs are primarily focused in the treatment of acute cardiovascular and secondarily in acute pulmonary diseases. Our lead product candidate, istaroxime, is a first-in-class, dual-acting agent being developed to improve cardiac function in patients with acute heart failure, or AHF, with a potentially differentiated safety profile from existing treatments. Istaroxime demonstrated significant improvement in both diastolic and systolic aspects of cardiac function and was generally well tolerated in two phase 2 clinical trials. Istaroxime has been granted Fast Track designation for the treatment of AHF by the U.S. Food and Drug Administration, or FDA. Based on the profile observed in our phase 2 clinical studies in AHF, where istaroxime significantly improved cardiac function and systolic blood pressure in acute decompensated heart failure patients, we initiated a phase 2 global clinical study to evaluate istaroxime for the treatment of early cardiogenic shock (Society for Cardiovascular Angiography and Interventions Stage B shock), a severe form of heart failure characterized by very low blood pressure and risk for hypoperfusion to critical organs. We believe that istaroxime has the potential to fulfill an unmet need in early cardiogenic shock. Our heart failure cardiovascular portfolio also includes sarco endoplasmic reticulum Ca2+ -ATPase 2a, or SERCA2a, activators which activate SERCA2a. This research program is evaluating these preclinical product candidates, including oral and intravenous SERCA2a activator heart failure compounds. As potential oral agents, these candidates would be developed for chronic heart failure. In addition, our cardiovascular drug product candidates include rostafuroxin, a novel product candidate for the treatment of hypertension in patients with a specific genetic profile. We are pursuing potential licensing arrangements and/or other strategic partnerships and do not intend to advance this product candidate without securing such an arrangement or partnership.

Our pulmonary product candidate portfolio consists of a KL4 surfactant platform to address a range of serious respiratory conditions in children and adults. KL4 surfactant has been in development as a liquid instillate for noninvasive delivery as an aerosol. In September 2020, the FDA accepted our investigational new drug, or IND, application for an open-label phase 2 pilot study to assess safety and tolerability in the COVID-19 acute respiratory distress syndrome, or ARDS, population and the ability of our KL4 surfactant liquid instillate to impact key respiratory parameters in the treatment of lung injury and ARDS resulting from severe acute respiratory syndrome coronavirus 2, or SARS-CoV-2, the causative agent in novel coronavirus, or COVID-19, infections. In January 2022, we completed enrollment of 20 patients in our phase 2 study of lucinactant (KL4 surfactant) for patients with severe COVID-19 associated ARDS and lung injury. The study demonstrated that intratracheal administration of reconstituted lyophilized lucinactant was generally safe and well tolerated. Lucinactant was safely administered to critically ill, mechanically ventilated patients with severe COVID-19 associated ARDS. Oxygenation and other physiological parameters were stable to improved after dosing, supporting the feasibility of this treatment approach to develop a potential treatment for critically ill patients with ARDS due to COVID-19 or other causes.

Previously, we were also developing AEROSURF (lucinactant for inhalation), a novel drug/medical device combination product for noninvasive delivery of aerosolized KL4 surfactant using our ADS technology for the treatment of respiratory distress syndrome, or RDS, in premature infants. We suspended all internal AEROSURF clinical activities in November 2020, because istaroxime, our lead product candidate, has become our primary focus for investment and execution as we believe development of istaroxime represents a greater value opportunity for us and our stockholders than development of KL4 surfactant. Since completing our phase 2 study of lucinactant (KL4 surfactant) for patients with severe COVID-19 associated ARDS and lung injury in January 2022, in order to preserve resources for the highest priority programs, we have begun to reduce costs that were not already transferred to our licensee in Asia, Lee's Pharmaceutical (HK) Ltd., or Lee's (HK), under the terms of our License, Development and Commercialization Agreement between us and Lee's (HK) dated as of June 12, 2017, as amended, or the Asia License Agreement. These costs include certain reductions in headcount dedicated to KL4 surfactant and the decommissioning of both our analytical and technical support laboratory, which previously conducted release testing of active pharmaceutical ingredients, or APIs, and supportive research for our lyophilized and aerosolized KL4 surfactant, and our medical device development laboratory, which was previously used to conduct development activities and testing for our ADS technologies. To support the future development of our KL4 surfactant platform in markets outside of Asia, including the U.S., we are pursuing one or more licensing transactions.

Our ability to advance our development programs is dependent upon our ability to secure additional capital in both the near and long-term, through public or private equity offerings; through potential strategic opportunities, including licensing agreements, drug product development and marketing collaboration arrangements, pharmaceutical research cooperation arrangements or other similar transactions in geographic markets, including the U.S., and/or through potential grants and other funding commitments from U.S. government agencies, in each case, if available. We have engaged with potential counterparties in various markets and will continue to pursue non-dilutive sources of capital as well as potential private and public offerings. There can be no assurance, however, that we will be able to identify and enter into public or private securities offerings on acceptable terms and in amounts sufficient to meet our needs or qualify for non-dilutive funding opportunities under any grant programs sponsored by U.S. government agencies, private foundations and/or leading academic institutions, or identify and enter into any strategic transactions that will provide the additional capital that we will require. If none of these alternatives is available, or if available, we are unable to raise sufficient capital through such transactions, we potentially could be forced to limit or cease our development activities, which would have a material adverse effect on our business, financial condition and results of operations.

Note 2 – Basis of Presentation

The consolidated financial statements are prepared in accordance with accounting principles generally accepted in the U.S., or US GAAP, and include accounts of Windtree Therapeutics, Inc. and its wholly owned subsidiaries. Intercompany balances and transactions have been eliminated in consolidation. All adjustments (consisting of normally recurring accruals) considered for fair presentation have been included.

The accompanying consolidated financial statements reflect the 1-for-3 reverse split of our common stock that was approved by our Board of Directors and controlling stockholders and made effective on April 29, 2020. All share and per share information herein that relates to our common stock prior to the effective date has been retroactively restated to reflect the reverse stock split.

WINDTREE THERAPEUTICS, INC. AND SUBSIDIARIES

Note 3 – Liquidity Risks and Management's Plans

We are subject to risks common to companies in the biotechnology industry, including but not limited to, the need for additional capital, risks of failure of preclinical and clinical studies, the need to obtain marketing approval and reimbursement for any drug product candidate that we may identify and develop, the need to successfully commercialize and gain market acceptance of our product candidates, dependence on key personnel, protection of proprietary technology, compliance with government regulations, development of technological innovations by competitors, and risks associated with our international locations and activities abroad, including but not limited to having foreign suppliers, manufacturers and clinical sites in support of our development activities.

We have incurred net losses since inception. Our net loss was $67.6 million and $32.6 million, respectively, for the years ended December 31, 2021 and 2020. Included in our net loss for the year ended December 31, 2021 is a $45.0 million loss on impairment of intangible assets related to rostafuroxin and a related $10.0 million deferred income tax benefit (*see,* Note 4 – Accounting Policies and Recent Accounting Pronouncements). We expect to continue to incur operating losses for at least the next several years. As of December 31, 2021, we had an accumulated deficit of $785.3 million. Our future success is dependent on our ability to fund and develop our product candidates, and ultimately upon our ability to attain profitable operations. We have devoted substantially all of our financial resources and efforts to research and development and general and administrative expense to support such research and development. Net losses and negative cash flows have had, and will continue to have, an adverse effect on our stockholders' equity and working capital, and accordingly, our ability to execute our future operating plans.

In March 2021, we received net proceeds of approximately $27.4 million related to a public offering of 9,230,500 units at a price per unit of $3.25. Each unit consisted of one share of our common stock and a warrant to purchase one share of common stock, or the March 2021 Warrants. The March 2021 Warrants were immediately exercisable for shares of common stock at a price of $3.60 per share and expire five years from the date of issuance.

We are party to an At-The-Market Offering Agreement with Ladenburg Thalmann & Co. Inc., or Ladenburg, pursuant to which we may offer and sell, from time to time at our sole discretion, up to a maximum of $10.0 million of shares of our common stock through Ladenburg as agent and/or principal through an at-the-market program, or the ATM Program. For the year ended December 31, 2021, we sold 2,116,944 shares of our common stock under the ATM Program resulting in aggregate gross proceeds to us of approximately $5.0 million and net proceeds of approximately $4.8 million (*see,* Note 10 – Stockholders' Equity).

As of December 31, 2021, we had cash and cash equivalents of $22.3 million and current liabilities of $4.9 million. As of March 31, 2022, we believe that we have sufficient resources available to support our development activities and business operations and satisfy our obligations into the first quarter of 2023. We do not have sufficient cash and cash equivalents as of the date of this Annual Report on Form 10-K to support our operations for at least the 12 months following the date that the financial statements are issued. These conditions raise substantial doubt about our ability to continue as a going concern through 12 months after the date that the financial statements are issued.

To alleviate the conditions that raise substantial doubt about our ability to continue as a going concern, management plans to secure additional capital, potentially through a combination of public or private equity offerings and strategic transactions, including potential licensing arrangements, alliances and drug product collaborations focused on specified geographic markets; however, none of these alternatives are committed at this time. There can be no assurance that we will be successful in obtaining sufficient funding on terms acceptable to us to fund continuing operations, if at all, or identify and enter into any strategic transactions that will provide the capital that we will require. If none of these alternatives is available, or if available, we are unable to raise sufficient capital through such transactions, we will not have sufficient cash resources and liquidity to fund our business operations for at least the next 12 months following the date that the financial statements are issued. The failure to obtain sufficient capital on acceptable terms when needed would have a material adverse effect on our business, results of operations, and financial condition. Accordingly, management has concluded that substantial doubt exists with respect to our ability to continue as a going concern through 12 months after the issuance of the accompanying financial statements.

The accompanying financial statements have been prepared on a going concern basis, which contemplates the realization of assets and satisfaction of liabilities in the normal course of business, and do not include any adjustments relating to recoverability and classification of recorded asset amounts or the amounts and classification of liabilities that might be necessary should we be unable to continue as a going concern.

Note 4 – Accounting Policies and Recent Accounting Pronouncements

Principles of Consolidation

The consolidated financial statements are prepared in accordance with US GAAP and include accounts of Windtree Therapeutics, Inc. and our wholly owned subsidiary, CVie Investments Limited and its wholly owned subsidiary, CVie Therapeutics Limited, or CVie Therapeutics,; and a presently inactive subsidiary, Discovery Laboratories, Inc. (formerly known as Acute Therapeutics, Inc.).

Goodwill and Intangible Assets

We record acquired identified intangibles, which includes intangible assets (such as goodwill and other intangibles), based on estimated fair value. The acquired in-process research and development, or IPR&D, assets are considered indefinite-lived intangible assets until completion or abandonment of the associated research and development efforts. IPR&D is not amortized but reviewed for impairment at least annually, or when events or changes in the business environment indicate that the carrying value may be impaired.

When testing our goodwill and indefinite-lived intangible assets for impairment, we can elect to perform a qualitative assessment to determine if it is more likely than not that the fair values of our reporting unit and indefinite-lived intangible assets are less than their respective carrying values. Such qualitative factors can include, among others, industry and market conditions, overall financial performance, and relevant entity-specific events. If we conclude based on our qualitative assessment that it is more likely than not that the fair value of our reporting unit or indefinite-lived intangible assets are less than their respective carrying values, we perform a quantitative assessment. When conducting our annual impairment test of goodwill and indefinite-lived intangible assets as of December 1, 2021, we elected to perform a quantitative assessment.

When performing the quantitative impairment assessment for our indefinite-lived IPR&D intangible assets, we estimate the fair values of the assets using the multi-period excess earnings method, or MPEEM. MPEEM is a variation of the income approach which estimates the fair value of an intangible asset based on the present value of the incremental after-tax cash flows attributable to the intangible asset. Significant factors considered in the calculation of IPR&D intangible assets include the risks inherent in the development process, including the likelihood of achieving commercial success and the cost and related time to complete the remaining development. Future cash flows for each project were estimated based on forecasted revenue and costs, taking into account the expected product life cycles, market penetration, and growth rates. Other significant estimates and assumptions inherent in this approach include (i) the amount and timing of the projected net cash flows associated with the IPR&D assets, (ii) the discount rate, which seeks to reflect the various risks inherent in the projected cash flows; and (iii) the tax rate, which considers geographic diversity of the projected cash flows. While we use the best available information to prepare our cash flows and discount rate assumptions, actual future cash flows could differ significantly based on the commercial success of the related drug candidates and market conditions which could result in future impairment charges related to our indefinite-lived intangible asset balances.

During the second quarter of 2021, we concluded an initial process to test the industry's interest in investing in our rostafuroxin drug candidate and were not able to secure a licensing transaction or other strategic opportunity at that time. Based on feedback received from potential licensing partners, we have determined that there is a need for an additional phase 2 clinical trial to demonstrate efficacy in non-Caucasian patients in treatment resistant hypertension. Due to these developments, and in connection with the preparation of the interim unaudited condensed consolidated financial statements as of and for the period ending June 30, 2021, we determined that the fair value of the IPR&D related to our rostafuroxin drug candidate was more likely than not less than its carrying value. As a result, we performed the required quantitative impairment assessment of the related intangible asset. We estimated the fair value of the asset using MPEEM and determined that the fair value as of June 30, 2021 was approximately $17.0 million. We then compared this fair value to the carrying value of approximately $54.8 million and recorded a loss on impairment of intangible assets of $37.8 million during the second quarter of 2021.

As part of our annual quantitative impairment assessment of indefinite-lived IPR&D intangible assets, we reassessed certain of the assumptions related to our rostafuroxin drug candidate due to the current macroeconomic conditions which have made it harder to secure the funding needed to conduct the additional phase 2 clinical trial and have therefore delayed our intended development of rostafuroxin. As a result, we concluded that the fair value of the IPR&D related to our rostafuroxin drug candidate was again less than its carrying value. We estimated the fair value of the asset using MPEEM and determined that the fair value as of December 1, 2021 was approximately $9.7 million. We then compared this fair value to the carrying value of approximately $17.0 million, and recorded an additional loss on impairment of intangible assets of $7.2 million in the fourth quarter of 2021. When combined with the loss on impairment of intangible assets recorded during the second quarter, we recorded a loss on impairment of intangible assets totaling $45.0 million within operating expenses in our consolidated statements of operations during the year ended December 31, 2021 . No events or changes in the business environment occurred during 2021 that would indicate that the fair value of the IPR&D related to our istaroxime drug candidate was impaired.

Goodwill represents the excess of the purchase price over the fair value of assets acquired and liabilities assumed in a business combination and is not amortized. It is reviewed for impairment at least annually or when events or changes in the business environment indicate that its carrying value may be impaired. Our company consists of one reporting unit. In order to perform the quantitative goodwill impairment test, we compare the estimated fair value of our reporting unit to its carrying value. If the fair value exceeds the carrying value, no further evaluation is required, and no impairment exists. If the carrying value exceeds the fair value, the difference between the carrying value and the fair value is recorded as an impairment loss, the amount of which may not exceed the total amount of goodwill. When performing our annual goodwill impairment assessment as of December 1, 2021, we estimated the fair value of our reporting unit based upon the quoted market price and related market capitalization of our common stock, adjusted for an estimated control premium. Based on the quantitative test performed, we determined that the fair value of our reporting unit exceeded its carrying value and no impairment exists.

The following table represents identifiable intangible assets and goodwill as of December 31, 2021 and 2020:

(in thousands)	December 31, 2021	December 31, 2020
Istaroxime drug candidate	$ 22,340	$ 22,340
Rostafuroxin drug candidate	9,730	54,750
Intangible assets	32,070	77,090
Goodwill	$ 15,682	$ 15,682

Foreign Currency Transactions

The functional currency for our foreign subsidiaries is US Dollars. We remeasure monetary assets and liabilities that are not denominated in the functional currency at exchange rates in effect at the end of each period. Gains and losses from the remeasurement of foreign currency transactions are recognized in other expense, net. Foreign currency transactions resulted in losses of approximately $0.3 million and $1.2 million, respectively, for the years ended December 31, 2021 and 2020.

Use of Estimates

The preparation of financial statements in conformity with US GAAP requires management to make estimates and assumptions that affect the reported amounts of assets and liabilities at the date of the financial statements and the reported amounts of revenues and expenses during the reporting period. Actual results could differ from those estimates.

Cash and Cash Equivalents

Cash and cash equivalents are held at domestic and foreign financial institutions and consist of liquid investments, money market funds, and U.S. Treasury notes with a maturity from date of purchase of 90 days or less that are readily convertible into cash.

WINDTREE THERAPEUTICS, INC. AND SUBSIDIARIES

Fair Value of Financial Instruments

Our financial instruments consist principally of cash and cash equivalents and restricted cash. The fair values of our cash equivalents are based on quoted market prices. The carrying value of cash equivalents is equal to their respective fair values at December 31, 2021 and 2020, respectively. Accounts payable and accrued expenses are carried at cost, which approximates fair value because of their short maturity. The carrying value of loans payable (including current installments) approximates fair value based on a comparison of interest rates on the loan to current market rates considering our credit risk.

Property and Equipment

Property and equipment are recorded at cost and depreciated using the straight-line method over the estimated useful lives of the assets (generally three to ten years). Leasehold improvements are amortized over the shorter of the estimated useful lives or the remaining term of the lease. Repairs and maintenance costs are charged to expense as incurred.

Restricted Cash

Restricted cash consists principally of a $140,000 certificate of deposit held by our bank as collateral for a letter of credit in the same notional amount held by our landlord to secure our obligations under our lease agreement dated May 26, 2004 for our headquarters location in Warrington, Pennsylvania and $14,000 in deposits held by our landlord for our offices in Taipei, Taiwan.

Leases

Leases are accounted for under Financial Accounting Standards Board, or FASB, Accounting Standards Codification, or ASC, Topic 842, *Leases*, or ASC 842. At the inception of an arrangement, we determine whether an arrangement is, or contains, a lease based on the unique facts and circumstances present in the arrangement. An arrangement is, or contains, a lease if the arrangement conveys the right to control the use of an identified asset for a period of time in exchange for consideration. Leases with a term greater than one year are generally recognized on the balance sheet as operating lease right-of-use assets and current and non-current operating lease liabilities, as applicable. It is our policy not to recognize on the balance sheet leases with terms of 12 months or less. We typically only include the initial lease term in our assessment of a lease arrangement. Options to extend a lease are not included in our assessment unless there is reasonable certainty that we will renew.

Operating lease liabilities and their corresponding operating lease right-of-use assets are recorded based on the present value of lease payments over the expected remaining lease term. Certain adjustments to the right-of-use asset may be required for items such as incentives received. The interest rate implicit in our leases is typically not readily determinable. As a result, we utilize our incremental borrowing rate, which reflects the fixed rate at which we could borrow on a collateralized basis the amount of the lease payments in the same currency, for a similar term, in a similar economic environment.

At the inception of a contract, we assess whether the contract is, or contains, a lease. The assessment is based on: (i) whether the contract involves the use of a distinct identified asset, (ii) whether we obtain the right to substantially all the economic benefit from the use of the asset throughout the period, and (iii) whether we have the right to direct the use of the asset.

We evaluate the classification of our leases as either finance leases or operating leases. A lease is classified as a finance lease if any one of the following criteria are met: the lease transfers ownership of the asset by the end of the lease term, the lease contains an option to purchase the asset that is reasonably certain to be exercised, the lease term is for a major part of the remaining useful life of the asset, the present value of the lease payments equals or exceeds substantially all of the fair value of the asset, or the leased asset is of such a specialized nature that it is expected to have no alternative use to the lessor at the end of the lease. A lease is classified as an operating lease if it does not meet any of these criteria. Currently, all of our leases are classified as operating leases.

Lease cost for our operating leases is recognized on a straight-line basis over the lease term. Included in lease cost are any variable lease payments incurred in the period that are not included in the initial lease liability and lease payments incurred in the period for any leases with an initial term of 12 months or less.

Long-lived Assets

Our long-lived assets, primarily consisting of property and equipment, are reviewed for impairment when events or changes in circumstances indicate that the carrying value of an asset may not be recoverable, or its estimated useful life has changed significantly. When the undiscounted cash flows of an asset are less than its carrying value, an impairment is recorded and the asset is written down to estimated value. No impairment was recorded during the years ended December 31, 2021 and 2020 as management believes there are no circumstances that indicate that the carrying value of the assets will not be recoverable.

Collaborative Arrangements

We account for collaborative arrangements in accordance with applicable accounting guidance provided in ASC Topic 808, *Collaborative Arrangements*. *See,* Note 12 – Collaboration, Licensing and Research Funding Agreements.

Severance

In July 2020, we entered into separation agreements with two executives, which provide that the former employees are entitled to receive: (i) a severance amount equal to the sum of their respective base salaries then in effect and their respective annual target bonus amounts, payable in equal installments through August 2021 and (ii) subject to certain exceptions, a pro rata bonus commensurate with the bonus of other contract executives for the year 2020, prorated for the number of days of their respective employment during 2020, and payable at the time that other contract executives are paid bonuses with respect to 2020. The severance amount related to the departure of these executives is approximately $0.9 million, was accrued at the date of the separations, and was paid ratably through August 2021. During the years ended December 31, 2021 and 2020, $0.5 million and $0.4 million, respectively, was paid and no further amounts are due as of December 31, 2021.

WINDTREE THERAPEUTICS, INC. AND SUBSIDIARIES

Restructured Debt Liability – Contingent Milestone Payment

In conjunction with the November 2017 restructuring and retirement of long-term debt (*see,* Note 9 – Restructured Debt Liability), we have established a $15.0 million long-term liability for contingent milestone payments potentially due under the Exchange and Termination Agreement dated as of October 27, 2017, or Exchange and Termination Agreement, between ourselves and affiliates of Deerfield Management Company L.P., or Deerfield. The liability has been recorded at full value of the contingent milestones and will continue to be carried at full value until the milestones are achieved and paid or milestones are not achieved and the liability is written off as a gain on debt restructuring.

Research and Development

We account for research and development expense by the following categories: (a) product development and manufacturing, (b) clinical, medical and regulatory operations, and (c) direct clinical and preclinical development programs. Research and development expense includes personnel, facilities, manufacturing and quality operations, pharmaceutical and device development, research, clinical, regulatory, other preclinical and clinical activities and medical affairs. Research and development costs are charged to operations as incurred in accordance with ASC Topic 730, *Research and Development*.

Stock-based Compensation

Stock-based compensation is accounted for under the fair value recognition provisions of ASC Topic 718, *Stock Compensation*, or ASC Topic 718. *See,* Note 11 – Stock Options and Stock-based Employee Compensation, for a detailed description of our recognition of stock-based compensation expense. The fair value of stock option grants is recognized evenly over the vesting period of the options or over the period between the grant date and the time the option becomes non-forfeitable by the employee, whichever is shorter.

Warrant Accounting

We account for common stock warrants in accordance with applicable accounting guidance provided in ASC Topic 815, *Derivatives and Hedging – Contracts in Entity's Own Equity*, or ASC Topic 815, as either derivative liabilities or equity instruments depending on the specific terms of the warrant agreement.

Income Taxes

We account for income taxes in accordance with ASC Topic 740, *Accounting for Income Taxes*, or ASC Topic 740, which requires the recognition of deferred tax liabilities and assets for the expected future tax consequences of temporary differences between financial statement carrying amounts and the tax basis of assets and liabilities.

We use a recognition threshold and measurement attribute for the financial statement recognition and measurement of a tax position taken or expected to be taken in a tax return. Because we have never realized a profit, management has fully reserved the net deferred tax asset since realization is not assured.

For the year ended December 31, 2021, we recorded a deferred income tax benefit of $10.0 million. The deferred income tax benefit recorded for this period relates solely to the reduction of the deferred tax liabilities as a result of the loss on impairment of intangible assets related to rostafuroxin.

Net Loss per Common Share

Basic net loss per common share is computed by dividing net loss by the weighted average number of common shares outstanding for the period. Diluted net loss per common share is computed by giving effect to all potentially dilutive securities outstanding for the period. For the years ended December 31, 2021 and 2020, the number of shares of common stock potentially issuable upon the exercise of certain stock options and warrants was 20.0 million and 9.1 million shares, respectively. As of December 31, 2021 and 2020, all potentially dilutive securities were anti-dilutive and therefore have been excluded from the computation of diluted net loss per common share.

We do not have any components of other comprehensive (loss) income.

Concentration of Suppliers

We currently obtain the APIs of our drug products from a single supplier. In addition, our drug products are produced at one contract manufacturer. These single source providers also perform various studies as well as quality control release and stability testing and other activities related to our development and manufacturing activities. At the present time these providers are located outside of the U.S. The loss of either the supplier of our APIs or our drug product contract manufacturer could have a material adverse effect on our operations.

Segment and Geographic Information

We currently operate in one operating segment, which is the research and development of products focused on acute cardiovascular and acute pulmonary diseases. We are managed and operated as one business. A single management team that reports to the Chief Executive Officer comprehensively manages the entire business. We do not operate separate lines of business with respect to our product candidates. We operate primarily in the U.S. and Asia. Long-lived assets, consisting of intangible assets of $32.1 million and goodwill of $15.7 million, were located outside the U.S. as of December 31, 2021.

WINDTREE THERAPEUTICS, INC. AND SUBSIDIARIES

COVID-19

The COVID-19 pandemic continues to evolve, and we continue to closely monitor its impact on our business and operations, including its continued impact on our clinical development plans and timelines, and financial condition. There has been intermittent impact of the pandemic in differing geographies, and there may be continued impact, particularly in light of the surge of new COVID-19 cases relating to new variants, such as the delta and omicron variants. As of the date of this Annual Report on Form 10-K, our operations, capital and financial resources and overall liquidity position and outlook have been impacted by COVID-19, primarily due to delays experienced in our operations, including in clinical study initiation and enrollment. The extended timelines have required us to expend more of our capital resources than planned to achieve our projected milestones. For example, our phase 2 study of istaroxime for early cardiogenic shock in heart failure patients experienced delays in trial initiation and enrollment in 2020 and 2021. The full extent, duration, or impact that the COVID-19 pandemic will have, directly or indirectly, on our financial condition and operations, including ongoing and planned clinical trials, will depend on future developments that are highly uncertain and cannot be accurately predicted. These potential future developments include new information that may emerge concerning the severity of the COVID-19 outbreak, the severity and transmissibility of new variants of the virus, information about any resurgences in one or more geographic locations where our current or intended clinical trial sites, our principal executive offices, research and development laboratories or manufacturing facilities are located, and the actions taken to contain it or treat its impact, which may include, among others, the timing and extent of government reopening activities and the economic impact on local, regional, national, and international markets. In addition, regional impact and responses to the COVID-19 pandemic have affected where a clinical trial could be executed and how various elements of the clinical trial are performed. Going forward, the pandemic could also impact how monitoring/auditing of clinical trial sites and data occur. The maintenance, or strategic re-implementation, of mitigating COVID-19 measures in one or more geographic locations where our clinical trial sites, principal executive offices, research and development laboratories or other facilities are located remains possible and if realized, we believe there could be further impact on the clinical development of our product candidates, which may include potential delays, halts or modifications to our ongoing and planned trials in 2022 and beyond.

We are not aware of any specific event or circumstance that would require us to further update our estimates, judgments or revise the carrying value of our assets or liabilities as of the date of issuance of these consolidated financial statements. These estimates may change, as new events occur and additional information is obtained.

Recent Accounting Pronouncements

In December 2019, the FASB issued Accounting Standards Update, or ASU, 2019-12, *Income Taxes (Topic 740): Simplifying the Accounting for Income Taxes*, or ASU 2019-12. ASU 2019-12 simplifies the accounting for income taxes by removing exceptions within the general principles of ASC Topic 740 regarding the calculation of deferred tax liabilities, the incremental approach for intra-period tax allocation, and calculating income taxes in an interim period. In addition, the ASU adds clarifications to the accounting for franchise tax (or similar tax), which is partially based on income, evaluating tax basis of goodwill recognized from a business combination, and reflecting the effect of any enacted changes in tax laws or rates in the annual effective tax rate computation in the interim period that includes the enactment date. The ASU was effective for fiscal years beginning after December 15, 2020, and interim periods within those fiscal years, with early adoption permitted. We adopted ASU 2019-12 on January 1, 2021, which did not have a material impact on our consolidated financial statements and related disclosures

Note 5 – Fair Value Measurements

Fair value is defined as the exchange price that would be received for an asset or paid to transfer a liability in the principal or most advantageous market for the asset or liability in an orderly transaction between market participants on the measurement date.

Valuation techniques used to measure fair value must maximize the use of observable inputs and minimize the use of unobservable inputs. The fair value hierarchy is based on three levels of inputs, of which the first two are considered observable and the last unobservable, as follows:

- Level 1 - Quoted prices in active markets for identical assets and liabilities.
- Level 2 - Inputs other than Level 1 that are observable, either directly or indirectly, such as quoted prices for similar assets or liabilities, quoted prices in markets that are not active, or other inputs that are observable or can be corroborated by observable market data for substantially the full term of the assets or liabilities.
- Level 3 - Unobservable inputs that are supported by little or no market activity and that are significant to the fair value of the assets or liabilities.

WINDTREE THERAPEUTICS, INC. AND SUBSIDIARIES

Fair Value on a Recurring Basis

The tables below categorize assets measured at fair value on a recurring basis as of December 31, 2021 and 2020:

(in thousands)	Fair Value December 31, 2021	Fair value measurement using Level 1	Level 2	Level 3
Cash equivalents:				
Money market funds	$ 21,104	$ 21,104	$ -	$ -
Total Assets	$ 21,104	$ 21,104	$ -	$ -

(in thousands)	Fair Value December 31, 2020	Fair value measurement using Level 1	Level 2	Level 3
Cash equivalents:				
U.S. Treasury notes	$ 9,101	$ 9,101	$ -	$ -
Money market funds	6,518	6,518	-	-
Total Assets	$ 15,619	$ 15,619	$ -	$ -

Fair Value on a Non-Recurring Basis

The table below categorizes assets measured at fair value on a non-recurring basis for the period presented:

(in thousands)	Fair Value December 31, 2021	Fair value measurement using Level 1	Level 2	Level 3
Intangible assets:				
Rostafuroxin drug candidate	$ 9,730	$ -	$ -	$ 9,730

The only asset or liability measured at fair value on a non-recurring basis during the year ended December 31, 2021 and 2020 was the IPR&D intangible asset related to our rostafuroxin drug candidate, which was recorded at its estimated fair value as a result of the impairment tests performed during 2021 (*see*, Note 4 – Accounting Policies and Recent Accounting Pronouncements – Goodwill and Intangible Assets).

Significant factors considered in estimating the fair value of the IPR&D intangible asset include the risks inherent in the development process, including the likelihood of achieving commercial success and the cost and related time to complete the remaining development. Future cash flows for the IPR&D asset were estimated based on forecasted revenue and costs, taking into account the expected product life cycle, market penetration, and growth rates. Other significant estimates and assumptions inherent in this approach include (i) the amount and timing of the projected net cash flows associated with the IPR&D asset; (ii) the discount rate, which seeks to reflect the various risks inherent in the projected cash flows; and (iii) the tax rate, which considers geographic diversity of the projected cash flows. Quantitative information about the significant unobservable inputs used in the fair value measurement of the IPR&D asset included a discount rate of approximately 19.0% and a tax rate of 30.0%. While we use the best available information to prepare our cash flows and discount rate assumptions, actual future cash flows could differ significantly based on the commercial success of the related drug candidate and market conditions which could result in future impairment charges related to the indefinite-lived intangible asset balance.

WINDTREE THERAPEUTICS, INC. AND SUBSIDIARIES

Note 6 – Property and Equipment

Property and equipment is comprised of the following:

(in thousands)	December 31, 2021	December 31, 2020
Manufacturing, laboratory & office equipment	$ 4,703	$ 4,591
Leasehold improvements	2,649	2,482
Furniture & fixtures	390	390
Subtotal	7,742	7,463
Accumulated depreciation and amortization	(6,731)	(6,539)
Property and equipment, net	$ 1,011	$ 924

Depreciation expense on property and equipment was $0.2 million for each of the years ended December 31, 2021 and 2020.

Note 7 – Accrued Expenses

Accrued expenses are comprised of the following:

(in thousands)	December 31, 2021	December 31, 2020
Research and development	$ 1,500	$ 1,207
Salaries, bonus and benefits	1,218	1,214
Severance	-	474
Professional fees	391	455
Manufacturing operations	46	41
Other	253	422
Total accrued expenses	$ 3,408	$ 3,813

Note 8 – Loans Payable

Current Portion

Loan Payable to Bank Direct Capital Finance

In June 2020, we entered into an insurance premium financing and security agreement with Bank Direct Capital Finance, or Bank Direct. Under the agreement, we financed $1.1 million of certain premiums at a 4.26% annual interest rate. Payments of approximately $117,000 were due monthly from July 2020 through March 2021. As of December 31, 2020, the outstanding principal of the loan was $0.4 million. The balance of the loan was repaid during the first quarter of 2021.

In June 2021, we entered into an insurance premium financing and security agreement with Bank Direct. Under the agreement, we financed $1.3 million of certain premiums at a 3.37% annual interest rate. Payments of approximately $147,000 are due monthly from July 2021 through March 2022. As of December 31, 2021, the outstanding principal of the loan was $0.3 million.

Non-Current Portion

O-Bank Co., Ltd. Credit Facility

In September 2016, CVie Therapeutics entered into a 12-month revolving credit facility of approximately $2.9 million with O-Bank Co., Ltd., or O-Bank, to finance operating activities, or the O-Bank Facility. The O-Bank Facility was later renewed and increased to approximately $5.8 million in September 2017. The O-Bank Facility was guaranteed by Lee's Pharmaceutical Holdings Limited, or Lee's Holdings, which pledged bank deposits in the amount of 110% of the actual borrowing amount. Interest, payable in cash on a monthly basis, was determined based on the 90-day Taipei Interbank Offer Rate, or TAIBOR, plus 0.91%. The O-Bank Facility expired on September 11, 2019 and the loans were set to mature six months after the expiration date, on March 11, 2020. In March 2020, the O-Bank Facility was amended, among other things, to extend the maturity date to March 2022, to decrease the total amount of the O-Bank Facility to approximately $5.0 million, to change the applicable interest rate to the TAIBOR plus 1.17% and to adjust the term to 24-month non-revolving.

In the second quarter of 2020, we were informed by Lee's Holdings of their desire to reduce the amount of pledged bank deposits with O-Bank by 50%. To remain in compliance with the terms of the O-Bank Facility, we repaid approximately $2.3 million of the outstanding principal in August 2020. In November 2020, Lee's Holdings committed to maintain the required level of pledged bank deposits with O-Bank through the date of full repayment of the O-Bank Facility. In June 2021, we repaid the remaining outstanding principal of the O-Bank Facility of approximately $2.5 million.

As of December 31, 2020, the outstanding principal of the O-Bank Facility was approximately $2.4 million and was classified as loans payable - non-current portion. There was no outstanding principal balance as of December 31, 2021, and the O-Bank Facility is no longer available to us.

Note 9 – Restructured Debt Liability

On October 27, 2017, we and Deerfield entered into the Exchange and Termination Agreement pursuant to which (i) promissory notes evidencing a loan with affiliates of Deerfield Management Company L.P., or the Deerfield Loan, in the aggregate principal amount of $25.0 million and (ii) warrants to purchase up to 8,333 shares of our common stock at an exercise price of $2,360.40 per share held by Deerfield were cancelled in consideration for (i) a cash payment in the aggregate amount of $2.5 million, (ii) 23,703 shares of common stock, representing 2% of fully-diluted shares outstanding (as defined in the Exchange and Termination Agreement) on the closing date, and (iii) the right to receive certain milestone payments based on achievement of specified AEROSURF development and commercial milestones, which, if achieved, could potentially total up to $15.0 million. In addition, a related security agreement, pursuant to which Deerfield held a security interest in substantially all of our assets, was terminated. We established a $15.0 million long-term liability for the contingent milestone payments potentially due to Deerfield under the Exchange and Termination Agreement. The liability has been recorded at the full value of the contingent milestones and will continue to be carried at full value until the milestones are achieved and paid or the milestones are not achieved and the liability is written off as a gain on debt restructuring.

As of December 31, 2021 and 2020, the restructured debt liability balance was $15.0 million.

Note 10 – Stockholders' Equity

March 2021 Public Offering

On March 23, 2021, we entered into an underwriting agreement with Oppenheimer & Co. Inc. as representative for the several underwriters named therein, relating to a public offering, or the March 2021 Offering, of an aggregate of 9,230,500 units with each unit consisting of one share of common stock and a warrant, or the March 2021 Warrants. The March 2021 Warrants were immediately exercisable for shares of common stock at a price of $3.60 per share and expire five years from the date of issuance. The shares of common stock and the March 2021 Warrants were immediately separable and were issued separately in the March 2021 Offering.

The closing of the March 2021 Offering occurred on March 25, 2021. The offering price to the public was $3.25 per unit resulting in gross proceeds to us of $30.0 million. After deducting underwriting discounts and commissions and estimated offering expenses payable by us, and excluding the proceeds, if any, from the exercise of the March 2021 Warrants issued pursuant to the March 2021 Offering, the net proceeds to us were approximately $27.4 million.

We have determined that the appropriate accounting treatment under ASC 480, *Distinguishing Liabilities from Equity*, or ASC 480, is to classify the common stock and the March 2021 Warrants issued in the March 2021 Offering as equity. We have also determined that the March 2021 Warrants are not in their entirety a derivative under the scope of ASC 815, *Derivatives and Hedging*, or ASC 815, due to the scope exception under ASC 815-10-15-74, nor are there any material embedded derivatives that require separate accounting. We allocated the net proceeds from the March 2021 Offering based on the relative fair value of the common stock and the March 2021 Warrants.

May 2020 Public Offering

On May 20, 2020, we entered into an underwriting agreement, or the Underwriting Agreement, with Ladenburg as representative for the several underwriters named therein, or collectively, the Underwriters, relating to a public offering, or the May 2020 Offering, of an aggregate of 2,758,620 units with each unit consisting of one share of our common stock and a warrant, or the May 2020 Warrants. The May 2020 Warrants are immediately exercisable for shares of common stock at a price of $7.975 per share and expire five years from the date of issuance. The shares of common stock and the May 2020 Warrants were immediately separable and were issued separately in the May 2020 Offering.

In addition, we granted the Underwriters a 45-day option, or the Overallotment Option, to purchase up to 413,793 additional shares of common stock and/or May 2020 Warrants to purchase up to 413,793 additional shares of common stock, which such Overallotment Option was exercised in full.

The closing of the May 2020 Offering occurred on May 22, 2020, inclusive of the Overallotment Option. The offering price to the public was $7.25 per unit. After deducting underwriting discounts and commissions and offering expenses of $2.8 million payable by us, and excluding the proceeds, if any, from the exercise of the May 2020 Warrants issued pursuant to the May 2020 Offering, the net proceeds to us were approximately $20.2 million.

We have determined that the appropriate accounting treatment under ASC 480 is to classify the common stock and the May 2020 Warrants issued in the May 2020 Offering as equity. We have also determined that the May 2020 Warrants are not in their entirety a derivative under the scope of ASC 815 due to the scope exception under ASC 815-10-15-74, nor are there any material embedded derivatives that require separate accounting. We allocated the net proceeds from the May 2020 Offering based on the relative fair value of the common stock and the May 2020 Warrants.

At-The-Market Program

On September 17, 2020, we entered into an At-The-Market Offering Agreement with Ladenburg pursuant to which we may offer and sell, from time to time at our sole discretion, up to a maximum of $10.0 million of shares of our common stock through Ladenburg as agent and/or principal through an at-the-market program, or the ATM Program. When we issue sales notices to Ladenburg, we designate the maximum amount of shares to be sold by Ladenburg daily and the minimum price per share at which shares may be sold. Ladenburg may sell shares by any method permitted by law deemed to be an "at-the-market offering" as defined in Rule 415(a)(4) under the Securities Act, or in privately negotiated transactions.

We agreed to pay Ladenburg a commission of 3% of the gross sales price of any shares sold pursuant to the ATM Program. The rate of compensation will not apply when Ladenburg acts as principal.

For the year ended December 31, 2021, we sold 2,116,944 shares of our common stock under the ATM Program resulting in aggregate gross proceeds to us of approximately $5.0 million and net proceeds of approximately $4.8 million.

As of March 31, 2022, approximately $5.0 million remains available under the ATM Program.

Warrant Amendments

On April 24, 2020, we and each of the holders of our Series F Warrants dated as of December 24, 2018, or the Series F Warrants, entered into Amendment No. 1 to the Series F Warrant to Purchase Common Stock whereby the expiration date of the Series F Warrants was extended from June 24, 2020 to December 24, 2020 in consideration for the holders agreeing to be bound by a lock-up provision with respect to any shares of our common stock or securities convertible, exchangeable or exercisable into shares of our common stock that are beneficially owned, held or acquired by the holders for a period of 90 days following the earlier of (i) the closing date of our next public offering of securities, or (ii) December 24, 2020. The lock-up provision commenced upon closing of the May 2020 Offering discussed above and has expired. The Series F Warrants expired on December 24, 2020.

On May 6, 2020, we and certain holders of our Series I Warrants dated as of December 6, 2019, or the Series I Warrants, entered into Amendment No. 1 to the Series I Warrant to Purchase Common Stock pursuant to which the exercise price of the Series I Warrants was amended from $12.09 to $9.67 if the Series I Warrants are exercised, in whole or in part, prior to December 5, 2021. In addition, the certain holders of the Series I Warrants agreed to be bound by a lockup provision with respect to any shares of our common stock or securities convertible, exchangeable or exercisable into shares of our common stock that are beneficially owned, held or acquired by such holders for a period of 90 days following the earlier of (i) the closing date of our next public offering of securities, or (ii) December 24, 2020. The lock-up provision commenced upon closing of the May 2020 Offering discussed above and has expired.

While there is no specific guidance that addresses the modification of an equity-classified contract, such as the amendments to the Series F Warrants and the Series I Warrants, it is the practice to determine the accounting for such modifications based on analogy to the share-based compensation guidance. The model for a modified share-based payment award that is classified as equity and remains classified in equity after the modification is addressed in ASC 718-20, *Compensation – Stock Compensation*, or ASC 718-20. Pursuant to that guidance, the incremental fair value from the modification (the change in the fair value of the instrument before and after the modification) is recognized as an expense in the income statement to the extent the modified instrument has a higher fair value.

For the Series F Warrants, the amendment to the terms related to a six-month extension of the expiration date and the incremental fair value from the modification was determined by comparing the Black-Scholes value before and after the modification. The amendment to the Series I Warrants related to a reduced exercise price for an 18-month period and the reversion after that period to the initial exercise price. As a result, the incremental fair value was determined by comparing the Black-Scholes value before the modification to a Monte Carlo valuation after the modification.

We have determined, based on the guidance in ASC 718-20 and our valuation of the Series F Warrants and the Series I Warrants, that the incremental fair value resulting from the modifications is $1.1 million, which was recorded as an increase to equity, with a corresponding expense recognized in the consolidated statement of operations as other expense for the year ended December 31, 2020.

Common Shares Reserved for Future Issuance

Common shares reserved for potential future issuance upon exercise of warrants

The chart below summarizes shares of our common stock reserved for future issuance upon the exercise of warrants:

(in thousands, except price per share data)	December 31, 2021	December 31, 2020	Exercise Price	Expiration Date
Investors - March 2021 financing	9,231	-	$ 3.60	03/25/26
Service Agreement - 2021 warrants	170	-	$ 8.25	02/09/24
Investors - May 2020 financing	3,155	3,155	$ 7.98	05/22/25
Investors - December 2019 financing	1,458	1,458	$ 12.09	12/06/24
Investors - AEROSURF	988	988	$ -	02/14/24
Investors - December 2018 financing - long-term	1,296	1,296	$ 12.15	12/04/23
Investors - December 2018 financing - short-term	-	-	$ 11.04	12/24/20
Battelle - 2018 payables restructuring agreement (1)	25	25	$ 19.50	12/07/23
Panacea Venture Management Company Ltd.	63	63	$ 12.00	07/02/23
LPH II Investments Limited	45	45	$ 16.56	04/04/25
Investors - February 2017 financing	117	117	$ 82.20	02/15/24
Investors - July 2015 financing	80	80	$ 588.00	07/22/22
Battelle - 2014 collaboration agreement	1	1	$ 4,200.00	10/10/24
Total	16,629	7,228		

(1) *See,* Note 12 – Collaboration, Licensing and Research Funding Agreements, for further details on the Battelle collaboration agreement.

Common shares reserved for potential future issuance upon granting of additional equity incentive awards

The 2020 Equity Incentive Plan, or the 2020 Plan, initially provided for up to a maximum of 1,535,500 shares of common stock to be available for issuance pursuant to stock-based awards granted under the 2020 Plan. The 2020 Plan is subject to automatic annual increases on January 1 of each year (beginning with January 1, 2022) of the lesser of (i) 4% of the number of shares of our common stock issued and outstanding on the last day of the immediately preceding fiscal year, and (ii) such smaller number of shares as determined by our board. *See,* Note 11 – Stock Options and Stock-based Employee Compensation.

As of December 31, 2021, we had 0.6 million shares available for potential future issuance under the 2020 Plan.

Note 11 – Stock Options and Stock-based Employee Compensation

Long-term Incentive Plans

On November 23, 2020, our Board of Directors adopted our 2020 Plan, which was subsequently approved by our majority stockholders by written consent on December 24, 2020 and became effective on January 20, 2021, or the Effective Date. On the Effective Date, the 2020 Plan replaced our 2011 long-term incentive plan, or the 2011 Plan, and the 2020 Plan became our primary plan for providing equity-based compensation to our eligible employees, consultants, and non-employee directors. Awards under the 2020 Plan may include stock options, stock appreciation rights, or SARs, restricted stock awards, or RSAs, restricted stock units, or RSUs, other performance and stock-based awards, and dividend equivalents.

As of December 31, 2021, there were 1.9 million shares of our common stock authorized under the 2020 Plan, of which 0.6 million shares remained available for issuance as of December 31, 2021.

The 2020 Plan is subject to automatic annual increases on January 1 of each year (beginning with January 1, 2022) of the lesser of (i) 4% of the number of shares of our common stock issued and outstanding on the last day of the immediately preceding fiscal year, and (ii) such smaller number of shares as determined by our board. The annual increase on January 1, 2022 was approximately 1.1 million shares.

An administrative committee, currently the Compensation Committee of the Board of Directors, or Committee delegates, may determine the types, the number of shares covered by, and the terms and conditions of, such awards. Eligible participants may include any of our employees, directors, advisors or consultants.

Stock options and RSUs outstanding and available for future issuance are as follows:

(in thousands)	December 31, 2021	December 31, 2020
Stock Options and RSUs Outstanding		
2020 Plan	1,256	-
2011 Plan	1,567	1,688
Non-Plan	564	215
Total Outstanding	3,387	1,903
Available for Future Grants under 2020 Plan	631	230

No SARs, RSAs, other performance and stock-based awards, or dividend equivalents have been granted under the 2020 Plan. Although individual grants may vary, option awards generally are exercisable upon vesting, vest in a series of three successive, equal installments beginning with the first anniversary of the grant date and have a 10-year term. Non-Plan stock options outstanding are in connection with the hiring of certain executive officers and other employees. Inducement grants were awarded in accordance with Nasdaq Listing Rule 5635(c)(4) and the inducement grants vest in a series of three successive, equal installments beginning with the first anniversary of the grant date and have a 10-year term.

A summary of activity under our long-term incentive plans is presented below:

(in thousands, except for weighted-average data)

Stock Options	Shares	Weighted-Average Exercise Price	Weighted-Average Remaining Contractual Term (In Yrs)
Outstanding at January 1, 2021	1,903	$ 15.57	
Granted	1,621	4.88	
Forfeited or expired	(137)	33.23	
Outstanding at December 31, 2021	3,387	$ 9.74	8.2
Vested and exercisable at December 31, 2021	1,685	$ 14.06	7.4
Vested and expected to vest at December 31, 2021	3,184	$ 9.78	8.2

During the year ended December 31, 2020, 35,000 RSUs vested at a weighted-average grant date fair value of $11.85. As of December 31, 2021 and 2020, there were no unvested RSUs.

Based upon application of the Black-Scholes option-pricing formula described below, the weighted-average grant-date fair value of options granted during the years ended December 31, 2021 and 2020 was $4.03 and $5.98, respectively. There were no RSUs granted during the years ended December 31, 2021 and 2020. The total intrinsic value of options outstanding, vested, and exercisable as of December 31, 2021 are each $0.

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Stock-Based Compensation

We recognized stock-based compensation expense in accordance with ASC Topic 718 of $7.2 million and $5.7 million, respectively, for each of the years ended December 31, 2021 and 2020.

Stock-based compensation expense was classified as follows:

(in thousands)	Year Ended December 31, 2021	2020
Research and development	$ 2,940	$ 2,098
General and administrative	4,298	3,586
Total	$ 7,238	$ 5,684

The fair value of each option award is estimated on the date of grant using the Black-Scholes option-pricing formula that uses assumptions noted in the following table. Expected volatilities are based upon the historical volatility of our common stock and other factors. We also use historical data and other factors to estimate option exercises, employee terminations and forfeiture rates. The risk-free interest rates are based upon the U.S. Treasury yield curve in effect at the time of the grant.

	Year Ended December 31, 2021	2020
Weighted average expected volatility	104%	103%
Weighted average expected term	6.7	7.0
Weighted average risk-free interest rate	0.49%	0.54%
Expected dividends	-	-

The total fair value of the underlying shares of the options vested during 2021 and 2020 is $6.7 million and $7.1 million, respectively. As of December 31, 2021, there was $4.2 million of total unrecognized compensation cost related to non-vested share-based compensation arrangements granted under the 2020 Plan and the 2011 Plan. That cost is expected to be recognized over a weighted-average vesting period of 1.8 years.

Note 12 – Collaboration, Licensing and Research Funding Agreements

Collaboration Agreement

Battelle Memorial Institute

In October 2014, we entered into a Collaboration Agreement with Battelle, or, as amended, the Battelle Collaboration Agreement, for the development of our new ADS for use in our phase 3 program. We had previously worked with Battelle, which has expertise in developing and integrating aerosol devices using innovative and advanced technologies, in connection with development of our phase 2 ADS used in the AEROSURF phase 2b clinical trial. Under the Battelle Collaboration Agreement, we and Battelle shared the costs of development for a three-stage development plan that included planning, executing the project plan and testing and completing verification and documentation of a new phase 3 ADS, putting us in a position to manufacture a new phase 3 ADS for use in the remaining AEROSURF development activities, including a potential phase 3 clinical program, and, if approved, initial commercial activities. We retained final decision-making authority over all matters related to the design, registration, manufacture, packaging, marketing, distribution and sale of the phase 3 ADS. We and Battelle shared the costs of the project plan equally. Battelle agreed to bear the cost of any cost overruns associated with the project plan and we agreed to bear the cost of any increase in cost resulting from changes in the scope of the product requirements. We also agreed that, if Battelle successfully completed the project plan in a timely manner, we would pay Battelle royalties equal to a low single-digit percentage of the worldwide net sales and license royalties on sales of AEROSURF for the treatment of RDS in premature infants, up to an initial aggregate limit of $25.0 million, which under a payment restructuring agreement (discussed below), was increased to $35.0 million. The Battelle Collaboration Agreement will end at the time we fulfill our payment obligations to Battelle, unless sooner terminated by a party as provided therein.

Licensing and Research Funding Agreements

Lee's Pharmaceutical (HK) Ltd.

In June 2017, we entered into the Asia License Agreement with Lee's (HK), an affiliate of Lee's Holdings, and thereafter amended it effective August 2017. Under the Asia License Agreement, as amended, we granted to Lee's (HK) an exclusive license with a right to sublicense (i) to develop, manufacture, and commercialize our KL4 surfactant products, including SURFAXIN, which was approved by the FDA in 2012 for RDS in premature infants, SURFAXIN LS™, the lyophilized dosage form of SURFAXIN, and AEROSURF, including the ADS, and (ii) to register and manufacture SURFAXIN and SURFAXIN LS for use in the licensed territory, which includes the People's Republic of China, or China, Hong Kong, Thailand, Taiwan and 12 other countries.

Under the Asia License Agreement, Lee's (HK) made an upfront payment to us of $1.0 million. We also may receive up to $35.8 million in potential clinical, regulatory and commercial milestone payments and will share in any sublicense income Lee's (HK) may receive at a rate equal to low double digits. In addition, Lee's (HK) is responsible for all costs and expenses in and for the licensed territory related to development activities, including a planned AEROSURF phase 3 clinical program, regulatory activities, and commercialization activities.

We will be eligible to receive tiered royalties based on a percent of Net Sales (as defined in the Asia License Agreement), depending on the product, in the range of high single to low-to-mid double-digit percentages. Royalties are payable on a country-by-country basis until the latest of (i) the expiration of the last valid patent claim covering the product in the country of sale, (ii) the expiration or revocation of any applicable regulatory exclusivity in the country of sale, and (iii) ten (10) years after the first commercial sale in the country of sale. Thereafter, in consideration of licensed rights other than patent rights, royalties shall continue for the commercial life of each product and, for the initial three years, shall be in the range of low-to-mid single digits. In addition, in the event that one or more generic products are introduced, the royalty rates will be reduced, subject to certain minimums if we are subject to continuing obligations at the time to pay royalties under our in-license agreements.

Under the Asia License Agreement, Lee's (HK) is responsible for all activities related to development, regulatory approval and commercialization of KL4 surfactant and drug/medical device combination products in the licensed territory. Lee's (HK) will hold the product licenses for all non-aerosolized products in the licensed territory and will seek regulatory approval initially for SURFAXIN and SURFAXIN LS for RDS. We will hold the product license in the licensed territory (except where prohibited by law) for all aerosolized products and will designate Lee's (HK) our exclusive agent and representative to develop and register AEROSURF and other aerosolized products in our name and on our behalf. Lee's (HK) also has agreed that, except as provided in the Asia License Agreement, for a period of ten (10) years beginning with the later of the first commercial sale of the first aerosolized product and the first commercial sale of the first non-aerosolized product in China, it will not develop, register, manufacture, or commercialize any product for the prevention and/or treatment of RDS in premature infants or other diseases and conditions in humans, in either case, that administers, utilizes or contains pulmonary surfactant without our prior written consent.

The Asia License Agreement is accounted for in accordance with ASC Topic 606 and constitutes a contract with a customer. All revenue related to the $1.0 million upfront payment was recognized as of the second quarter of 2019 and no future material performance obligations are due. Regulatory and commercialization milestones were excluded from the transaction price, as all milestone amounts were fully constrained under the guidance. Consideration related to sales-based milestones and royalties will be recognized when the related sales occur, provided that the reported sales are reliably measurable and that we have no remaining performance obligations, as such sales were determined to relate predominantly to the license granted to Lee's (HK) and therefore have also been excluded from the transaction price. We will re-evaluate the transaction price in each reporting period and as uncertain events are resolved or other changes in circumstances occur.

On March 18, 2020, we entered into the Term Sheet with Lee's (HK) pursuant to which Lee's (HK) agreed to provide financing to fund the development of AEROSURF for the period April 1, 2020 through September 30, 2020 and make payments of up to $3.9 million (which was reduced to $2.8 million under specified circumstances) prior to September 1, 2020. In August 2020, we entered into a Project Financing Agreement with Lee's (HK), or the PF Agreement with Lee's (HK), formalizing the terms of the Term Sheet, and under which we received payments totaling $2.8 million through October 2020. Pursuant to the PF Agreement, Lee's (HK) agreed to pay additional amounts to be set forth in an updated development budget to be agreed between the parties by September 1, 2020 and updated every six months thereafter, to fund the continued development of AEROSURF and to be paid with the payment schedule to be set forth in each updated development budget. In partial satisfaction of our obligations under the PF Agreement, we agreed to pay Lee's (HK) 50% of any Commercialization Net Revenues (as defined in the PF Agreement) up to an amount that is equal to 125% of the Project Expenses (as defined in the PF Agreement) funded by Lee's (HK). On November 12, 2020, Lee's (HK) provided notice of termination of additional funding under the PF Agreement, and we and Lee's (HK) revised our plans for the continued development of AEROSURF. Lee's (HK) agreed to continue the development of AEROSURF in Asia at its own cost. Lee's (HK) agreed to fund an additional $1.0 million to us in 2021 for certain transition and analytical services to be provided by us with respect to the development of AEROSURF, which will be considered "Project Expenses" under the terms of the PF Agreement. In 2021, we received payments totaling $1.0 million from Lee's (HK) and no further amounts are due under the PF Agreement as of December 31, 2021.

Since the 2018 acquisition of CVie Investments Limited and CVie Therapeutics, istaroxime has become our primary focus for investment and execution due to what we believe represents a greater potential value opportunity for us and our stockholders. Since completing our phase 2 study of lucinactant (KL4 surfactant) for patients with severe COVID-19 associated ARDS and lung injury in January 2022, in order to preserve resources for the highest priority programs, we have begun to reduce costs not already transferred to our licensee in Asia, Lee's (HK), under the terms of our Asia License Agreement. These costs include certain reductions in headcount dedicated to KL4 surfactant and the decommissioning of both our analytical and technical support laboratory, which previously conducted release testing of APIs and supportive research for our lyophilized and aerosolized KL4 surfactant, and our medical device development laboratory, which was previously used to conduct development activities and testing for our ADS technologies. To support the future development of our KL4 surfactant platform in markets outside of Asia, including the U.S., we are pursuing one or more licensing transactions.

To repay the funds provided under the terms of the PF Agreement, until such time as we have repaid 125% of the amounts funded by Lee's (HK) for the development of AEROSURF, we will pay to Lee's (HK) 50% of all revenue amounts and payments received by us for any sale, divestiture, license or other development and/or commercialization of the KL4/AEROSURF patent portfolio, excluding (i) payments for bona fide research and development services; (ii) reimbursement of patent expenses and (iii) all amounts paid to us under the Asia License Agreement, minus certain deductions and certain reductions for any payments made by us with respect to third party intellectual property not previously funded by Lee's (HK).

As of December 31, 2021 and 2020, the liability balance related to the payments under the PF Agreement was $3.8 million and $2.8 million, respectively, and is recorded in other liabilities.

We have determined that the Term Sheet and the PF Agreement are within the scope of ASC 730-20, *Research and Development Arrangements*, or ASC 730-20. We concluded that there has not been a substantive and genuine transfer of risk related to the Term Sheet or the PF Agreement as there is a presumption that we are obligated to repay Lee's (HK) based on the significant related party relationship that existed at the time the parties entered into the Term Sheet and the PF Agreement, including Lee's (HK)'s ownership of outstanding shares of our common stock.

We have determined that the appropriate accounting treatment under ASC 730-20 is to record the proceeds received from Lee's (HK) as cash and cash equivalents, as we have the ability to direct the usage of funds, and a long-term liability on our consolidated balance sheet when received. The liability will remain on the balance sheet until we repay such amounts as a result of any revenues and payments received by us for any sale, divestiture, license or other development and/or commercialization of the KL4/AEROSURF patent portfolio.

We have also determined that the Term Sheet and the PF Agreement are not in their entirety a derivative under the scope of ASC 815, due to the scope exception under ASC 815-10-15-59, nor are there any embedded derivatives that require separate accounting.

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Philip Morris USA Inc. and Philip Morris Products S.A.

Under license agreements with Philip Morris USA Inc., or PMUSA, and Philip Morris Products S.A., or PMPSA, we hold exclusive worldwide licenses to the ADS technology for use with pulmonary surfactants (alone or in combination with any other pharmaceutical compound(s)) for all respiratory diseases and conditions (the foregoing uses in each territory, the Exclusive Field), and an exclusive license in the U.S. for use with certain non-surfactant drugs to treat specified respiratory indications in humans in designated hospital settings. We generally are obligated to pay royalties at a rate equal to a low single-digit percent of sales of products sold in the Exclusive Field (as defined in the license agreements) in the territories, including sales of aerosol devices that are not based on the ADS technology (unless we exercise our right to terminate the license with respect to a specific indication). While there is no legal obligation under the agreements to make minimum royalty payments, in the event we do not make quarterly minimum royalty payments, PMUSA and PMPSA can terminate the agreements. In making such payments, we are entitled to a reduction of future royalties in an amount equal to the excess of any minimum royalty paid over royalties actually earned in prior periods.

Johnson & Johnson and Ortho Pharmaceutical Corporation

We, Johnson & Johnson, or J&J, and its wholly owned subsidiary, Ortho Pharmaceutical Corporation, are parties to a license agreement granting to us an exclusive worldwide license to the J&J KL4 surfactant technology. Under the license agreement, we are obligated to pay fees of up to $2.5 million in the aggregate upon our achievement of certain milestones, primarily upon receipt of marketing regulatory approvals for certain designated products. We have paid $1.0 million to date for milestones that have been achieved. In addition, the license agreement requires that we make royalty payments at different rates, depending upon type of revenue and country, in amounts in the range of a high single-digit percent of net sales (as defined in the license agreement) of licensed products sold by us or sublicensees, or, if greater, a percentage of royalty income from sublicensees in the low double digits.

Laboratorios del Dr. Esteve, S.A.

We have a strategic alliance with Laboratorios del Dr. Esteve, S.A., or Esteve, for the development, marketing and sales of a broad portfolio of potential KL4 surfactant products in Andorra, Greece, Italy, Portugal, and Spain. Antonio Esteve, Ph.D., a principal of Esteve, served as a member of our Board of Directors from May 2002 until January 2013. Esteve will pay us a transfer price on sales of our KL4 surfactant products. We will be responsible for the manufacture and supply of all of the covered products and Esteve will be responsible for all sales and marketing in the territory. Esteve is obligated to make stipulated cash payments to us upon our achievement of certain milestones, primarily upon receipt of marketing regulatory approvals for the covered products. In addition, Esteve has agreed to contribute to phase 3 clinical trials for the covered products by conducting and funding development performed in the territory. As part of a 2004 restructuring in which Esteve returned certain rights to us in certain territories, or the Former Esteve Territories, we agreed to pay Esteve 10% of any cash up front and milestone fees (up to a maximum aggregate of $20.0 million) that we receive in connection with any strategic collaborations for the development and/or commercialization of certain of our KL4 surfactant products in the Former Esteve Territories.

Universita degli Studi di Milano-Bicocca

Effective April 13, 2015, CVie Therapeutics, entered into an Agreement for Scientific Collaboration with the Universita degli Studi di Milano-Bicocca, or Bicocca, in Milan, Italy, focused on defining the role of SERCA2a and phospholamban, or PLN, in modulating cardiac contraction, and discovering new small molecules to modulate SERCA2a activity or new drugs for treating chronic and acute human heart failure. The term of the collaboration agreement would have expired after three years but was extended for approximately an additional year, with option for further renewal.

Under the collaboration agreement, intellectual property resulting from the collaboration, including patents and know-how, will be jointly owned by the parties. For the development of any new SERCA2a compounds and diagnostic products suitable for further clinical development, we have the option to purchase Bicocca's interest for up to 12 months after the filing of a patent application. If the option is not exercised, then the parties shall remain joint owners and each can use the intellectual property with consent of the other on terms to be defined. If we exercise an option, we have agreed to pay Bicocca (corresponding to stage of development): (i) € 0.1 million upon completion and the proof of concept of biological efficacy for new compounds modulating the SERCA2a activity caused by PLN mutations; and (ii) € 1.5 million upon obtaining marketing authorization in the U.S., EU, or China of new compounds with the corresponding companion diagnostic assay. We have also agreed to pay royalties for any purchased intellectual property arising out of the collaboration in the range of a low- to mid-single digit percent of net sales for any products sold in any country for a period of ten years from the date of the first commercial sale.

On March 19, 2021, we entered into an Agreement for Scientific Collaboration, or the New SERCA2a Agreement, with Bicocca, which extends our collaboration. The New SERCA2a Agreement amends and restates the recently expired terms of the prior collaboration agreement. Under the New SERCA2a Agreement, we will provide Bicocca with approximately € 0.2 million for research activities and to cover laboratory space and operation costs. Results obtained from the collaboration will be jointly owned by the parties. However, Bicocca will assign to us its interest in patent applications and patents covering any new SERCA2a compounds and diagnostic products suitable for further clinical development. We have agreed to pay Bicocca (corresponding to stage of development): (i) € 25,000 for execution of an assignment to us of Bicocca's interest in the patent at issue, (ii) € 75,000 for new SERCA2a compounds developed up to phase 1 studies in humans upon the completion and availability of the proof of concept of biological efficacy of new compounds on modulating the SERCA2a activity in cell-free systems, or its functional counterpart in isolated cells and (iii) € 1.5 million upon obtaining marketing authorization in the U.S., EU, or China of new compounds with the corresponding companion diagnostic assay. We have also agreed to pay royalties on products generated from the collaboration in the range of a fraction of a single digit to a low single digit percent of net sales for any products sold in any country for a period of ten years from the date of the first commercial sale or until the expiry of patent(s) covering the products. In connection with our research activities, Bicocca agreed to provide us exclusive use of a research laboratory for the collaboration, and nonexclusive access to a physiology laboratory within the university. Bicocca serves as our primary location in Milan.

Note 13 – Related Party Transactions

Lee's Pharmaceutical Holdings Limited

As of December 31, 2021 and 2020, Lee's Holdings beneficial ownership of our issued and outstanding shares of common stock was 17% and 29%, respectively.

We entered into the following transactions with Lee's Holdings during 2021 and 2020:

- In March 2020, we entered into the Term Sheet, with Lee's (HK), pursuant to which Lee's (HK) had agreed to provide financing for the development of AEROSURF. In August 2020, we entered into the PF Agreement with Lee's (HK), formalizing the terms of the Term Sheet, under which we received payments of $2.8 million in 2020 and payments of $1.0 million in 2021. As of December 31, 2021 and 2020, the liability balance related to the payments under the PF Agreement was $3.8 million and $2.8 million, respectively, and is recorded in other liabilities. The liability will remain on the balance sheet until we repay such amounts as a result of any revenues and payments received by us for any sale, divestiture, license or other development and/or commercialization of the KL4/AEROSURF patent portfolio. No further amounts are due under the PF Agreement as of December 31, 2021 (*see*, Note 12 – Collaboration, Licensing and Research Funding Agreements – Lee's Pharmaceutical (HK) Ltd.);

- We incurred $0.2 million in research and development expenses for services provided by an affiliate of Lee's Holdings to our wholly owned subsidiary, CVie Therapeutics, during 2020; and

- On December 31, 2021, we entered into a Master Manufacturing and Supply Agreement with an affiliate of Lee's Holdings for the manufacture of our istaroxime drug product candidate.

Panacea Venture

As of December 31, 2021 and 2020, Panacea's beneficial ownership of our issued and outstanding shares of common stock was 8% and 14%, respectively.

James Huang, who in connection with the CVie Acquisition in December 2018 was appointed as a director and Chairman of our Board, is a founding and Managing Partner to Panacea Venture, or Panacea.

During 2020, we entered into the following transactions with Panacea:

- In May 2020, Panacea was an investor of $2.0 million in the May 2020 Offering (s*ee,* Note 10 – Stockholders' Equity – May 2020 Public Offering);

Note 14 – Litigation

We are not aware of any pending or threatened legal actions that would, if determined adversely to us, have a material adverse effect on our business and operations.

We have from time to time been involved in disputes and proceedings arising in the ordinary course of business, including in connection with the conduct of our clinical trials. In addition, as a public company, we are also potentially susceptible to litigation, such as claims asserting violations of securities laws. Any such claims, with or without merit, if not resolved, could be time-consuming and result in costly litigation. There can be no assurance that an adverse result in any future proceeding would not have a potentially material adverse effect on our business, results of operations and financial condition.

Note 15 – Income Taxes

The components of the benefit for income taxes for the years ended December 31, 2021 and 2020 is as follows:

	December 31,	
(in thousands)	**2021**	**2020**
Current expense (benefit):		
Federal	$ -	$ -
State	-	-
Foreign	-	-
Total current expense (benefit)	-	-
Deferred expense (benefit):		
Federal	-	-
State	-	-
Foreign	(9,987)	-
Total deferred expense (benefit)	(9,987)	-
Total income tax expense (benefit)	$ (9,987)	$ -

For the year ended December 31, 2021, we recorded a deferred income tax benefit of $10.0 million. The deferred income tax benefit recorded for this period relates solely to the reduction of the deferred tax liabilities as a result of the loss on impairment of intangible assets related to rostafuroxin.

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The reconciliation of the income tax benefit computed at the federal statutory rates to our recorded tax benefit for the years ended December 31, 2021 and 2020 is as follows:

(in thousands)	December 31, 2021	December 31, 2020
Income tax benefit, statutory rates	$ (16,301)	$ (6,837)
State taxes on income, net of federal benefit	(1,390)	(125)
Net operating loss expirations	2,184	1,835
Research and development tax credit	94	(1,213)
Foreign rate differential	462	22
Employee related and other	(186)	193
Interest related	-	34
Income tax expense / (benefit), statutory rates	(15,137)	(6,091)
Valuation allowance	5,150	6,091
Income tax benefit, net	$ (9,987)	$ -

The tax effects of temporary differences that give rise to deferred tax assets and deferred tax liabilities as of December 31, 2021 and 2020, are as follows:

(in thousands)	December 31, 2021	December 31, 2020
Long-term deferred assets:		
Net operating loss carryforwards (federal and state)	$ 187,905	$ 183,793
Research and development tax credit	18,538	18,632
Compensation expense on stock	4,568	3,525
Other accrued	2,006	1,811
Depreciation	115	112
Total long-term deferred tax assets	213,132	207,873
Long-term deferred liabilities:		
IPR&D	(7,114)	(16,778)
Total long-term deferred tax liabilities	(7,114)	(16,778)
Valuation allowance	(213,132)	(207,873)
Deferred tax liabilities, net	$ (7,114)	$ (16,778)

We are in a net deferred tax liability position as of December 31, 2021 and 2020. Because we have never realized a profit, management has fully reserved the net deferred tax asset since realization is not assured. It is our policy to classify interest and penalties recognized on uncertain tax positions as a component of income tax expense. There was neither interest nor penalties accrued as of December 31, 2021 and 2020, nor were any incurred in 2021 or 2020.

At December 31, 2021 and 2020, we had available carryforward net operating losses for federal tax purposes of $644.6 million and $631.9 million, respectively, research and development tax credit carryforward of $17.4 million and $17.2 million, respectively and orphan drug tax credit carryforwards of $1.1 million and $1.4 million, respectively. Of the of $644.6 million of federal net operating loss carryforwards, $80.8 million can be carried forward indefinitely. The remaining Federal net operating loss, research and development tax credit carryforwards and orphan drug credit carryforward will continue to expire through 2040.

At December 31, 2021 and 2020, we had available carryforward losses of approximately $598.9 million and $585.3 million, respectively, for state tax purposes. Of the $598.9 million state tax carryforward losses, $595.4 million is associated with the state of Pennsylvania, with the remainder associated with the other seven (7) states within which we have established tax nexus.

Future realization of the tax benefits of existing temporary differences and net operating loss carryforwards ultimately depends on the existence of sufficient taxable income within the carryforward period. As of December 31, 2021 and 2020, we performed an evaluation to determine whether a valuation allowance was needed. We considered all available evidence, both positive and negative, which included the results of operations for the current and preceding years. We determined that it was not possible to reasonably quantify future taxable income and determined that it is more likely than not that all of the deferred tax assets will not be realized. Accordingly, we maintained a full valuation allowance as of December 31, 2021 and 2020.

Under Internal Revenue Code Section 382, if a corporation undergoes an “ownership change,” the corporation’s ability to use its pre-change NOL carryforwards and other pre-change tax attributes to offset its post-change income may be limited. We have not completed a study to assess whether an “ownership change” has occurred or whether there have been multiple ownership changes since we became a “loss corporation” as defined in Section 382. Future changes in our stock ownership, which may be outside of our control, may trigger an “ownership change.” In addition, future equity offerings or acquisitions that have equity as a component of the purchase price could result in an “ownership change.” If an “ownership change” has occurred or does occur in the future, utilization of the NOL carryforwards or other tax attributes may be limited, which could potentially result in increased future tax liability to us.

Utilization of net operating loss, or NOL, and research and development, or R&D, credit carryforwards may be subject to a substantial annual limitation under Section 382 of the Internal Revenue Code of 1986 due to ownership change limitations that have occurred previously or that could occur in the future. These ownership changes may limit the amount of NOL and R&D credit carryforwards that can be utilized annually to offset future taxable income and tax, respectively. There also could be additional ownership changes in the future, which may result in additional limitations in the utilization of the carryforward NOLs and credits.

A full valuation allowance has been provided against our deferred tax assets and, if a future assessment requires an adjustment, an adjustment would be offset by an adjustment to the valuation allowance. Thus, there would be no impact to the consolidated balance sheets or statements of operations if an adjustment were required.

Note 16 – Leases

Our operating leases consist primarily of facility leases for our operations in Warrington, Pennsylvania and Taipei, Taiwan.

We maintain our corporate headquarters and operations in Warrington, Pennsylvania. The facility serves as the main operating facility for drug and device development, regulatory, analytical technical services, research and development, and administration. We also maintain offices in Taipei, Taiwan where we perform certain manufacturing development and preclinical activities related to our cardiovascular drug product candidates.

In January 2021, we entered into a lease amendment to extend the term of our Warrington, Pennsylvania lease for a period of five years commencing on March 1, 2022 and expiring on February 28, 2027.

Throughout the term of our leases, we are responsible for paying certain variable lease costs, in addition to the rent, as specified in the lease, including a proportionate share of applicable taxes, operating expenses and utilities.

The following table contains a summary of the lease costs recognized under ASC 842 and other information pertaining to our operating leases for the years ended December 31, 2021 and 2020:

(in thousands)	Year Ended December 31, 2021	2020
Operating lease cost	$ 857	$ 826
Variable lease cost	45	29
Total lease cost	$ 902	$ 855
Other Information		
Operating cash flows used for operating leases	$ 734	$ 895
Operating lease liabilities arising from obtaining right-of-use assets	$ 2,141	$ 249
Weighted average remaining lease term (in years)	4.8	1.3
Weighted average incremental borrowing rate	7.12%	9.00%

Future minimum lease payments under our non-cancelable operating leases as of December 31, 2021, are as follows:

(in thousands)	December 31, 2021
2022	$ 689
2023	575
2024	560
2025	570
2026	581
Thereafter	97
Total lease payments	3,072
Less imputed interest	(473)
Total operating lease liabilities at December 31, 2021	$ 2,599

Note 17 – Subsequent Events

In January 2022, in order to focus our resources on the development of our istaroxime pipeline, we began to reduce costs related to KL4 surfactant that were not already transferred to our licensee in Asia, Lee's (HK), under the terms of our Asia License Agreement. These costs include certain reductions in headcount dedicated to KL4 surfactant and the decommissioning of both our analytical and technical support laboratory, which previously conducted release testing of APIs and supportive research for our lyophilized and aerosolized KL4 surfactant, and our medical device development laboratory, which was previously used to conduct development activities and testing for our ADS technologies. The total severance cost for impacted employees is approximately $0.4 million and is expected to be paid through September 30, 2022. In addition, we have approximately $0.7 million of net book value related to manufacturing and laboratory equipment related to KL4 surfactant, and we are currently evaluating the disposition or alternative future use of these assets.

EMPLOYMENT AGREEMENT

This Employment Agreement (the "Agreement") is made as of July 1, 2021, by and between **WINDTREE THERAPEUTICS, INC.**, a Delaware corporation (the "Company"), and **DIANE CARMAN** ("Executive"), subject to the terms and conditions defined in this Agreement.

WHEREAS, the Company and Executive desire that Executive be employed by the Company to act as the Company's General Counsel, subject to the terms and conditions set forth in this Agreement. Executive's employment shall also be subject to such policies and procedures as the Company may from time to time implement so long as such policies are not less favorable to Executive than the terms of this Agreement;

NOW, THEREFORE, in consideration of the covenants contained herein, and for other valuable consideration, the Company and Executive hereby agree as follows:

1. Certain Definitions. Certain definitions used herein shall have the meanings set forth on Exhibit A attached hereto.

2. Term of the Agreement. The term ("Term") of this Agreement shall commence on the date first above written and shall continue until terminated as provided in Section 7 hereof. Upon the occurrence of a Change of Control during the term of this Agreement, including any extensions hereof, this Agreement shall automatically be extended until the end of the Effective Period. On the Date of Termination, Executive acknowledges Executive shall immediately be deemed to have resigned all employment and related job duties and responsibilities with the Company, including, without limitation any and all positions on any committees or boards of the Company or any affiliated company. Executive agrees to sign all reasonable documentation evidencing the foregoing as may be presented to Executive for signature by the Company.

3. Executive's Duties and Obligations.

(a) Duties. Executive shall serve as the Company's Senior Vice President & General Counsel. Executive shall be responsible for all duties customarily associated with a General Counsel in a publicly-traded company.

(b) Location of Employment. Executive's principal place of business shall be at the Company's headquarters. In addition, Executive acknowledges and agrees the performance by Executive of Executive's duties shall require frequent travel including, without limitation, overseas travel from time to time.

(c) Proprietary Information and Inventions Matters. In consideration of the covenants contained herein, Executive has executed and agrees to be bound by the Company's standard form of Proprietary Information, Inventions, Non-Solicitation and Non-Competition Agreement (the "Confidentiality Agreement"), which is attached to this Agreement as Exhibit B. Executive shall comply at all times with the terms and conditions of the Confidentiality Agreement and all other reasonable policies of the Company governing its confidential and proprietary information.

4. Devotion of Time to Company's Business.

(a) Full-Time Efforts. During Executive's employment with the Company, Executive shall devote substantially all of Executive's business time, attention and efforts to the proper performance of Executive's implicit and explicit duties and obligations hereunder to the reasonable satisfaction of the Company.

(b) No Other Employment or Providing Services. During Executive's employment with the Company, Executive shall not, except as otherwise provided herein, directly or indirectly, render any services of a commercial or professional nature to any other person or organization, whether for compensation or otherwise, without the prior written consent of the Executive Committee or the Board of Directors of the Company (the "Board").

5. Compensation and Benefits.

(a) Base Compensation. During the Term, the Company shall pay to Executive base annual compensation ("Base Salary") of $375,000.00 payable in accordance with the Company's regular payroll practices and less all required withholdings. Executive's Base Salary shall be reviewed annually and may be increased based on an assessment of Executive's performance, the performance of the Company, inflation, the then prevailing salary scales for comparable positions and other relevant factors; provided, however, any increase in Base Salary shall be solely within the discretion of the Company. Executive's Base Salary shall not be subject to reduction from the level in effect hereunder from time to time, other than pursuant to a salary reduction program of general application to contract executives of the Company, which absent mutual agreement shall not to exceed 20% of salary.

(b) Annual Bonuses. During the Term, Executive shall be eligible for such year-end bonus, which may be paid in either cash or equity, or both, based upon a target Annual Bonus Amount of 40% of Base Salary, as may be awarded solely at the discretion of the Compensation Committee of the Board after consultation with the Company's Chief Executive Officer, provided, the Company shall be under no obligation whatsoever to pay such discretionary year-end bonus for any year. Any such equity bonus shall contain such rights and features as are typically afforded to other Company employees of a similar level in connection with comparable equity bonuses awarded by the Company. For clarification, Executive's bonus shall not be pro-rated for 2021, and Executive shall receive the bonus she would have received had she started with the Company on January 1, 2021. Except as otherwise provided in Section 7, in order for the Executive to receive payment of any such annual bonus, the Executive must be employed by the Company as of the date the annual bonus is paid.

(c) Equity. As soon as practicable, the Company will recommend to the Compensation Committee of the Board of Directors (the "Committee") that Executive be granted an option to acquire 150,000 shares of WINT stock (the "Option"). One-third of the number of shares of Common Stock subject to the Option shall vest and become exercisable on the first anniversary of the date Executive commences her employment with the Company (the "Start Date"), another one-third of the Option shall vest and become exercisable on the second anniversary of the Start Date, and the final one-third of the Option shall vest and become exercisable on the third Anniversary of the Start Date, all subject to Executive's continuing employment on the stated Start Date anniversaries. In addition, the Executive shall be eligible for annual option *or other stock* grants as may be awarded solely at the discretion of the Board of Directors or Committee, provided that neither the Board of Directors nor Committee shall be under any obligation whatsoever to grant such discretionary options awards. Any options issued to Executive after the Option shall be governed by the Company's 2020 Long-Term Incentive Plan and the Employee Option Agreement(s) under the 2020 Long-Term Incentive Plan *or any amendments thereto* by which they are issued. The Option award is an "inducement" material to Executive's entry into employment with the Company within the meaning of Rule 5635(c)(4) of the NASDAQ Marketplace Rules, and will be granted outside of the Company's 2020 Long-Term Incentive Plan pursuant to an award agreement, but will be governed in all respects as if issued under the 2020 Long-Term Incentive Plan.

(d) Signing Bonus. Upon execution of this Agreement, Company will pay you a signing bonus in the amount of five thousand dollars ($5,000).

(e) Benefits. During the Term, Executive shall be entitled to participate in all employee benefit plans, programs and arrangements made available generally to the Company's senior executives or to its employees on substantially the same basis such benefits are provided to such executives of a similar level or to other employees (including, without limitation, profit-sharing, savings and other retirement plans (e.g. a 401(k) plan) or programs, medical, dental, hospitalization, vision, short-term and long-term disability and life insurance plans or programs, accidental death and dismemberment protection, travel accident insurance, and any other employee welfare benefit plans or programs may be sponsored by the Company from time to time, including any plans or programs that supplement the above-listed types of plans or programs, whether funded or unfunded); provided, however, nothing in this Agreement shall be construed to require the Company to establish or maintain any such plans, programs or arrangements.

(f) Vacations. During the Term, Executive shall be entitled to 20 days paid vacation per year, or such greater amount as may be earned under the Company's standard vacation policy, to be earned ratably throughout the year. Vacation days may only be carried from one year to the next in accordance with the Company vacation policy. Executive will also be granted up to five (5) personal days per year and six (6) sick days per year, which will accrue on a monthly basis in accordance with company policy and be prorated in year one based upon your date of hire.

(g) Reimbursement of Business Expenses. Executive is authorized to incur reasonable expenses in carrying out Executive's duties and responsibilities under this Agreement and the Company shall reimburse Executive for all such expenses, in accordance with reasonable policies of the Company.

6. Change of Control Benefits. Notwithstanding any provision to the contrary in any of the Company's long-term incentive plans or in any stock option or restricted stock agreement between the Company and Executive, all shares of stock and all options to acquire Company stock held by Executive shall accelerate and become fully vested and, with respect to restricted stock, all restrictions shall be lifted upon the Change of Control Date, provided Executive is actively employed by the Company on such Change of Control Date.

7. Termination of Employment.

(a) Termination by the Company for Cause or Termination by Executive without Good Reason, Death or Disability.

(i) In the event of a termination of Executive's employment by the Company for Cause, a termination by Executive without Good Reason, or in the event this Agreement terminates by reason of the death or Disability of Executive, Executive shall be entitled to any unpaid compensation accrued through the last day of Executive's employment, a lump sum payment in respect of all accrued but unused vacation days at Executive's Base Salary in effect on the date such vacation was earned, and payment of any other amounts owing to Executive but not yet paid, less any amounts owed by Executive to the Company. Executive shall not be entitled to receive any other compensation or benefits from the Company whatsoever (except as and to the extent the continuation of certain benefits is required by law).

(ii) In the case of a termination due to death or Disability, notwithstanding any provision to the contrary in any stock option or restricted stock agreement between the Company and Executive, all shares of stock and all options to acquire Company stock held by Executive shall accelerate and become fully vested upon the Date of Termination (and all options shall thereupon become fully exercisable) and the Company will pay any earned but unpaid annual bonus for the fiscal year preceding the Termination Date.

(b) Termination by the Company without Cause or by Executive for Good Reason. If (x) Executive's employment is terminated by the Company other than for Cause, death or Disability (i.e., without Cause) or (y) Executive terminates employment with Good Reason, then Executive will receive the amounts set forth in Section 7(a)(i), any other additional benefits then due or earned in accordance with generally applicable employee benefit plans and programs of the Company, and, on the condition the Executive signs a separation agreement containing a plenary release of claims in a form acceptable to the Company within fifty (50) days after the Date of Termination (or such shorter period specified in such plenary release) and such plenary release becomes final, binding and irrevocable, the Executive shall also be entitled to receive the following from the Company:

(i) Any earned but unpaid annual bonus for the fiscal year preceding the Termination Date and a pro rata bonus equal to the Annual Bonus Amount multiplied by the fraction obtained by dividing the number of days in the year through the Date of Termination by 365, which amount shall be paid when the Company's other employment contract executives are paid;

(ii) An amount equal to the Executive's Base Salary then in effect (determined without regard to any reduction in such Base Salary constituting Good Reason), payable in equal installments in accordance with the Company's regular payroll schedule, from the Date of Termination to the date that is 12 months after the Date of Termination (the "Severance Period"); provided, however, each installment payable before the plenary release becomes final, binding and irrevocable shall not be paid to the Executive until such plenary release becomes final, binding and irrevocable;

(iii) During the Severance Period, if Executive elects to continue Company medical benefits through the Consolidated Omnibus Budget Reconciliation Act of 1985 ("COBRA"), the Company shall continue to pay the Company's costs of such benefits as if Executive continued under the same plans and on the same terms and conditions as an active employee of the Company. Company's obligation under this Section 7(b)(iii) shall terminate if Executive becomes eligible for group health plan benefits under a subsequent employer's plan or a spouse's employer plan; and

(iv) Upon the date the plenary release becomes final, binding and irrevocable, notwithstanding any provision to the contrary in any stock option or restricted stock agreement between the Company and the Executive, all vested stock options to acquire Company stock and all other similar equity awards held by the Executive as of the Date of Termination shall continue to be exercisable during the Severance Period, subject to earlier exercise in the event of a Change of Control pursuant to the plan governing such awards.

Notwithstanding the foregoing, if Executive engages in a material breach of any provision of this Agreement or the Executive's Confidentiality Agreement during the Severance Period, and such breach is not cured within 5 business days, then the Company's continuing obligations under this Section 7(b) shall cease as of the date of the breach and the Executive shall be entitled to no further payments hereunder.

(c) Termination in connection with a Change of Control. If Executive's employment is terminated by the Company without Cause or by Executive for Good Reason during the Effective Period, and on the condition the Executive signs a separation agreement containing a plenary release of claims in a form acceptable to the Company within fifty (50) days after the Date of Termination (or such shorter period specified in such plenary release) and such plenary release becomes final, binding and irrevocable, then Executive shall be entitled to receive the following from the Company:

(i) All amounts and benefits described in Section 7(a)(i) above and any other additional benefits then due or earned in accordance with generally applicable employee benefit plans and programs of the Company;

(ii) Within 10 days after the Date of Termination, any earned but unpaid annual bonus for the fiscal year preceding the Termination Date;

(iii) Within 10 days after the Date of Termination, a lump sum cash payment in an amount equal to 1.5 times the sum of (A) Executive's Base Salary then in effect (determined without regard to any reduction in such Base Salary constituting Good Reason) and (B) the Annual Bonus Amount; provided, however, if Executive's employment is terminated prior to the consummation of a Change of Control but under circumstances that would cause the Change of Control Date to precede the date the Change of Control is consummated, such amount will be paid in equal installments in accordance with the Company's regular payroll schedule over the Severance Period described in Section 7(b)(ii);

(iv) If Executive elects to continue Company medical benefits under COBRA, for a period of 18 months following the Date of Termination (the "Benefit Period"), the Company shall continue to pay the Company's costs of such benefits as Executive elects to continue under the same plans and on the same terms and conditions as such benefits are provided to active employees of the Company. Company's obligation under this Section 7(b)(iii) shall terminate if Executive becomes eligible for group health plan benefits under a subsequent employer's plan or a spouse's employer plan;

(v) Notwithstanding any provision to the contrary in any stock option or restricted stock agreement between the Company and Executive, all shares of stock and all options to acquire Company stock held by Executive shall accelerate and become fully vested upon the Date of Termination (and all options shall thereupon become fully exercisable), and all stock options shall continue to be exercisable for the remainder of their stated terms, subject to earlier exercise pursuant to the plan governing such awards.

Notwithstanding the foregoing, if Executive engages in a material breach of any provision of this Agreement or Executive's Confidentiality Agreement during the Severance Period, and such breach is not cured within five business days after receipt from the Company of notice thereof, then the Company's continuing obligations under this Section 7(c) shall cease as of the date of the breach and the Executive shall be entitled to no further payments or benefits hereunder.

8. Notice of Termination.

(a) Any termination of Executive's employment by the Company for Cause, or by Executive for Good Reason shall be communicated by a Notice of Termination to the other party hereto given in accordance with Section 12. For purposes of this Agreement, a "Notice of Termination" means a written notice which: (i) is given at least 10 days prior to the Date of Termination (at least 30 days in the case of Notice of Termination given by Executive for Good Reason), (ii) indicates the specific termination provision in this Agreement relied upon, (iii) to the extent applicable, sets forth in reasonable detail the facts and circumstances claimed to provide a basis for termination of Executive's employment under the provision so indicated, and (iv) specifies the employment termination date. The failure to set forth in the Notice of Termination any fact or circumstance which contributes to a showing of Good Reason or Cause will not waive any right of the party giving the Notice of Termination hereunder or preclude such party from asserting such fact or circumstance in enforcing its rights hereunder.

(b) A termination of employment of Executive will not be deemed to be for Good Reason unless Executive gives the Notice of Termination provided for herein within 30 days after Executive has actual knowledge of the act or omission of the Company constituting such Good Reason and Executive gives the Company a 30-day cure period to rectify or correct the condition or event that constitutes Good Reason and Executive terminates her employment within 30 days of the date Company's failure to cure deadline has expired.

9. Mitigation of Damages. Executive will not be required to mitigate damages or the amount of any payment or benefit provided for under this Agreement by seeking other employment or otherwise. Except as otherwise provided in Sections 7(b)(iv) and 7(c)(iv), the amount of any payment or benefit provided for under this Agreement will not be reduced by any compensation or benefits earned by Executive as the result of self-employment or employment by another employer or otherwise.

10. Excess Parachute Excise Tax.

(a) Anything in this Agreement to the contrary notwithstanding, in the event it shall be determined any payment, award, benefit or distribution (including any acceleration) by the Company or any entity which effectuates a transaction described in Section 280G(b)(2)(A)(i) of the Code to or for the benefit of Executive (whether pursuant to the terms of this Agreement or otherwise, but determined without regard to any additional payments required under this Section 10) (a "Payment") would be subject to the excise tax imposed by Section 4999 of the Code or any interest or penalties are incurred with respect to such excise tax by Executive (such excise tax, together with any such interest and penalties, are hereinafter collectively referred to as the "Excise Tax"), the Company will automatically reduce such Payments to the extent, but only to the extent, necessary so no portion of the remaining Payments will be subject to the Excise Tax, unless the amount of such Payments the Executive would retain after payment of the Excise Tax and all applicable Federal, state and local income taxes without such reduction would exceed the amount of such Payments the Executive would retain after payment of all applicable Federal, state and local taxes after applying such reduction. Unless otherwise elected by the Executive, to the extent permitted under Code Section 409A, the Company shall reduce or eliminate the payments by first reducing or eliminating any cash severance benefits (with the payments to be made furthest in the future being reduced first), then by reducing or eliminating any accelerated vesting of stock options or similar awards, then by reducing or eliminating any accelerated vesting of restricted stock or similar awards, then by reducing or eliminating any other remaining Payments; provided, no such reduction or elimination shall apply to any non-qualified deferred compensation amounts (within the meaning of Section 409A of the Code) to the extent such reduction or elimination would accelerate or defer the timing of such payment in a manner that does not comply with Section 409A of the Code.

(b) All determinations required to be made under this Section 10, including the assumptions to be utilized in arriving at such determination, shall be made by the Company's independent auditors or such other professional firm or certified public accounting firm of national standing reasonably as may be designated by the Company (the "Accounting Firm") which shall provide detailed supporting calculations both to the Company and Executive within 15 business days of the receipt of notice from Executive there has been a Payment, or such earlier time as is requested by the Company. All fees and expenses of the Accounting Firm shall be borne solely by the Company. If the Accounting Firm determines no Excise Tax is payable by Executive, it shall furnish Executive with a written opinion to such effect, and to the effect that failure to report the Excise Tax, if any, on Executive's applicable federal income tax return will not result in the imposition of a negligence or similar penalty. Any determination by the Accounting Firm shall be binding upon the Company and Executive.

11. Legal Fees. All reasonable legal fees and related expenses (including costs of experts, evidence and counsel) paid or incurred by Executive pursuant to any claim, dispute or question of interpretation relating to this Agreement shall be paid or reimbursed by the Company if Executive is successful on the merits pursuant to a legal judgment or arbitration. Except as provided in this Section 11, each party shall be responsible for its own legal fees and expenses in connection with any claim or dispute relating to this Agreement.

12. Notices. All notices, requests, demands and other communications hereunder shall be in writing and shall be deemed to have been duly given if delivered by hand or mailed within the continental United States by first class certified mail, return receipt requested, postage prepaid, addressed as follows:

If to the Board or the Company:	**If to Executive:**
Windtree Therapeutics, Inc.	Diane Carman
2600 Kelly Road, Suite 100	162 Brooklea Road
Warrington, PA 18976 USA	Bryn Mawr, PA 19010
Attention: President	
With a copy to: Legal@windtreetx.com	With a copy to: Dcarman610@gmail.com

Addresses may be changed by written notice sent to the other party at the last recorded address of that party.

13. Withholding. The Company shall be entitled to withhold from payments due hereunder any required federal, state or local withholding or other taxes.

14. Entire Agreement. This Agreement contains the entire agreement between the parties with respect to the subject matter hereof and supersedes the Offer Letter and all other prior agreements, written or oral, with respect thereto.

15. Arbitration.

(a) If the parties are unable to resolve any dispute or claim relating directly or indirectly to this Agreement or any dispute or claim between Executive and the Company or its officers, directors, agents, or employees (a "Dispute"), then either party may require the matter to be settled by final and binding arbitration by sending written notice of such election to the other party clearly marked "Arbitration Demand." Such Dispute shall be arbitrated in accordance with the terms and conditions of this Section 15. Notwithstanding the foregoing, either party may apply to a court of competent jurisdiction for a temporary restraining order, a preliminary injunction, or other equitable relief to preserve the status quo or prevent irreparable harm.

(b) The Dispute shall be resolved by a single arbitrator in an arbitration administered by the American Arbitration Association in accordance with its Employment Arbitration Rules and judgment upon the award rendered by the arbitrator may be entered in any court having jurisdiction thereof. The decision of the arbitrator shall be final and binding on the parties, and specific performance giving effect to the decision of the arbitrator may be ordered by any court of competent jurisdiction.

(c) Nothing contained herein shall operate to prevent either party from asserting counterclaim(s) in any arbitration commenced in accordance with this Agreement, and any such party need not comply with the procedural provisions of this Section 15 in order to assert such counterclaim(s).

(d) The arbitration shall be filed with the office of the American Arbitration Association ("AAA") located in Philadelphia, Pennsylvania or such other AAA office as the parties may agree upon (without any obligation to so agree). The arbitration shall be conducted pursuant to the Employment Arbitration Rules of AAA as in effect at the time of the arbitration hearing, such arbitration to be completed in a 60-day period. In addition, the following rules and procedures shall apply to the arbitration:

(i) The arbitrator shall have the sole authority to decide whether or not any Dispute between the parties is arbitrable and whether the party presenting the issues to be arbitrated has satisfied the conditions precedent to such party's right to commence arbitration as required by this Section 15.

(ii) The decision of the arbitrator, which shall be in writing and state the findings, the facts and conclusions of law upon which the decision is based, shall be final and binding upon the parties, who shall forthwith comply after receipt thereof. Judgment upon the award rendered by the arbitrator may be entered by any competent court. Each party submits itself to the jurisdiction of any such court, but only for the entry and enforcement to judgment with respect to the decision of the arbitrator hereunder.

(iii) The arbitrator shall have the power to grant all legal and equitable remedies (including, without limitation, specific performance) and award compensatory and punitive damages if authorized by applicable law.

(iv) Except as provided in Section 11, the parties shall bear their own costs in preparing for and participating in the resolution of any Dispute pursuant to this Section 15, and the costs of the arbitrator(s) shall be equally divided between the parties.

(v) Except as provided in the last sentence of Section 15(a), the provisions of this Section 15 shall be a complete defense to any suit, action or proceeding instituted in any federal, state or local court or before any administrative tribunal with respect to any Dispute arising in connection with this Agreement. Any party commencing a lawsuit in violation of this Section 15 shall pay the costs of the other party, including, without limitation, reasonable attorney's fees and defense costs.

16. Miscellaneous.

(a) Governing Law. This Agreement shall be interpreted, construed, governed and enforced according to the laws of the Commonwealth of Pennsylvania without regard to the application of choice of law rules.

(b) Amendments. No amendment or modification of the terms or conditions of this Agreement shall be valid unless in writing and signed by the parties hereto.

(c) Severability. If one or more provisions of this Agreement are held to be invalid or unenforceable under applicable law, such provisions shall be construed, if possible, so as to be enforceable under applicable law, or such provisions shall be excluded from this Agreement and the balance of the Agreement shall be interpreted as if such provision were so excluded and shall be enforceable in accordance with its terms.

(d) Binding Effect. This Agreement shall be binding upon and inure to the benefit of the beneficiaries, heirs and representatives of Executive (including the Beneficiary) and the successors and assigns of the Company. The Company shall require any successor (whether direct or indirect, by purchase, merger, reorganization, consolidation, acquisition of property or stock, liquidation, or otherwise) to all or substantially all of its assets to assume and agree to perform this Agreement in the same manner and to the same extent the Company would be required to perform this Agreement if no such succession had taken place. Regardless whether such agreement is executed, this Agreement shall be binding upon any successor of the Company in accordance with the operation of law and such successor shall be deemed the Company for purposes of this Agreement.

(e) Successors and Assigns. Except as provided in Section16(d) in the case of the Company, or to the Beneficiary in the case of the death of Executive, this Agreement is not assignable by any party and no payment to be made hereunder shall be subject to anticipation, alienation, sale, transfer, assignment, pledge, encumbrance or other charge.

(f) Remedies Cumulative; No Waiver. No remedy conferred upon either party by this Agreement is intended to be exclusive of any other remedy, and each and every such remedy shall be cumulative and shall be in addition to any other remedy given hereunder or now or hereafter existing at law or in equity. No delay or omission by either party in exercising any right, remedy or power hereunder or existing at law or in equity shall be construed as a waiver thereof, and any such right, remedy or power may be exercised by such party from time to time and as often as may be deemed expedient or necessary by such party in such party's sole discretion.

(g) Survivorship. Notwithstanding anything in this Agreement to the contrary, all terms and provisions of this Agreement by their nature extend beyond the termination of this Agreement shall survive such termination.

(h) Entire Agreement. This Agreement sets forth the entire agreement of the parties hereto with respect to the subject matter contained herein and supersedes all prior agreements, promises, covenants or arrangements, whether oral or written, with respect thereto.

(i) Counterparts. This Agreement may be executed in two or more counterparts, each of which shall constitute an original, but all of which, when taken together, shall constitute one document.

17. No Contract of Employment. Nothing contained in this Agreement will be construed as a right of Executive to be continued in the employment of the Company, or as a limitation of the right of the Company to discharge Executive with or without Cause.

18. Section 409A of the Code. The intent of the parties is that payments and benefits under this Agreement comply with, or be exempt from, Section 409A of the Code and, accordingly, to the maximum extent permitted, this Agreement shall be construed and interpreted in accordance with such intent. Executive's termination of employment (or words to similar effect) shall not be deemed to have occurred for purposes of this Agreement unless such termination of employment constitutes a "separation from service" within the meaning of Code Section 409A and the regulations and other guidance promulgated thereunder.

(a) Notwithstanding any provision to the contrary in this Agreement, if Executive is deemed on the date of Executive's termination to be a "specified employee" within the meaning of that term under Code Section 409A(a)(2)(B) and using the identification methodology selected by the Company from time to time, or if none, the default methodology set forth in Code Section 409A, then with regard to any payment or the providing of any benefit constitutes "non-qualified deferred compensation" pursuant to Code Section 409A and the regulations issued thereunder is payable due to Executive's separation from service, to the extent required to be delayed in compliance with Code Section 409A(a)(2)(B), such payment or benefit shall not be made or provided to Executive prior to the earlier of (i) the expiration of the six (6) month period measured from the date of Executive's separation from service, and (ii) the date of Executive's death (the "Delay Period"). On the first day of the seventh month following the date of Executive's separation from service or, if earlier, on the date of Executive's death, all payments delayed pursuant to this Section 18(a) shall be paid or reimbursed to Executive in a lump sum, and any remaining payments and benefits due to Executive under this Agreement shall be paid or provided in accordance with the normal payment dates specified for them herein.

(b) To the extent any reimbursement of costs and expenses provided for under this Agreement constitutes taxable income to Executive for Federal income tax purposes, such reimbursements shall be made no later than December 31 of the calendar year next following the calendar year in which the expenses to be reimbursed are incurred. With regard to any provision herein that provides for reimbursement of expenses or in-kind benefits, except as permitted by Code Section 409A, (i) the right to reimbursement or in-kind benefits is not subject to liquidation or exchange for another benefit, and (ii) the amount of expenses eligible for reimbursement, or in-kind benefits, provided during any taxable year shall not affect the expenses eligible for reimbursement, or in-kind benefits to be provided, in any other taxable year.

(c) If any amount under this Agreement is to be paid in two or more installments, for purposes of Code Section 409A each installment shall be treated as a separate payment.

19. Executive Acknowledgement. Executive hereby acknowledges (a) Executive has read and understands the provisions of this Agreement, (b) Executive has been given the opportunity for Executive's legal counsel to review this Agreement, (c) the provisions of this Agreement are reasonable, and (d) Executive has received a copy of this Agreement.

[signature page to follow]

IN WITNESS WHEREOF, the parties hereto have caused this Employment Agreement to be executed as of the date first above written.

WINDTREE THERAPEUTICS, INC.	**DIANE CARMAN**
By: /s/ Craig E. Fraser	/s/ Diane Carman
Name: Craig E. Fraser	Diane Carman, Executive
Title: President and CEO	
Date:	Dated:

EXHIBIT A

(a) "**Annual Bonus Amount**" means the current year's target annual bonus amount for the Executive.

(b) "**Beneficiary**" means any individual, trust or other entity named by Executive to receive the payments and benefits payable hereunder in the event of the death of Executive. Executive may designate a Beneficiary to receive such payments and benefits by completing a form provided by the Company and delivering it to the General Counsel of the Company. Executive may change her designated Beneficiary at any time (without the consent of any prior Beneficiary) by completing and delivering to the Company a new beneficiary designation form. If a Beneficiary has not been designated by Executive, or if no designated Beneficiary survives Executive, then the payment and benefits provided under this Agreement, if any, will be paid to Executive's estate, which shall be deemed to be Executive's Beneficiary.

(c) "**Cause**" means: (i) Executive's willful and continued neglect of Executive's duties with the Company (other than as a result of Executive's incapacity due to physical or mental illness), after a written demand for substantial performance is delivered to Executive by the Company which specifically identifies the manner in which the Company believes Executive has neglected her duties; (ii) the final conviction of Executive of, or an entering of a guilty plea or a plea of no contest by Executive to, a felony; (iii) Executive's willful engagement in illegal conduct or gross misconduct which is materially and demonstrably injurious to the Company; or (iv) the debarment of Executive by the FDA.

For purposes of this definition, no act or failure to act on the part of Executive shall be considered "willful" unless it is done, or omitted to be done, by Executive in bad faith or without a reasonable belief the action or omission was in the best interests of the Company. Any act, or failure to act, based on authority given pursuant to a resolution duly adopted by the Board, or the advice of counsel to the Company, will be conclusively presumed to be done, or omitted to be done, by Executive in good faith and in the best interests of the Company.

(d) "**Change of Control**" means the occurrence of any one of the following events:

(i) any "person" (as defined in Sections 13(d) and 14(d) of the Securities Exchange Act of 1934 (the "Exchange Act")), other than the Company, any trustee or other fiduciary holding securities under an employee benefit plan of the Company, an underwriter temporarily holding securities pursuant to an offering of such securities or any corporation owned, directly or indirectly, by the stockholders of the Company in substantially the same proportions as their ownership of stock of the Company, directly or indirectly (x) acquires "beneficial ownership" (as defined in Rule 13d-3 under the Exchange Act) of securities representing more than 50% of the combined voting power of the Company's then outstanding securities or; (y) acquires within a 12 consecutive month period "beneficial ownership" (as defined in Rule 13d-3 under the Exchange Act) of securities representing 35% of the combined voting power of the Company's then outstanding securities;

(ii) persons who comprise a majority of the Board are replaced during any 12 consecutive month period by directors whose appointment or election is not endorsed by a majority of the members of the Board before the date of such appointment or election;

(iii) the consummation of a reorganization, merger, statutory share exchange, consolidation or similar corporate transaction (each, a "Business Combination") other than a Business Combination in which all or substantially all of the individuals and entities who were the beneficial owners of the Company's voting securities immediately prior to such Business Combination beneficially own, directly or indirectly, 50% or more of the combined voting power of the voting securities of the entity resulting from such Business Combination (including, without limitation, an entity which as a result of the Business Combination owns the Company or all or substantially all of the Company's assets either directly or through one or more subsidiaries) in substantially the same proportions as their ownership of the Company's voting securities immediately prior to such Business Combination; or

(iv) any "person" (as defined in Sections 13(d) and 14(d) of the Exchange Act) acquires all or substantially all of the assets of the Company within any 12 consecutive month period.

Notwithstanding the foregoing, none of the foregoing events shall constitute a Change of Control of the Company unless such event also constitutes a change in ownership of the Company within the meaning of Treasury Regulation Section 1.409A-3(i)(5)(v), a change in the effective control of the Company within the meaning of Treasury Regulation Section 1.409A-3(i)(5)(vi) or a change in ownership of a substantial portion of the assets of the Company within the meaning of Treasury Regulation Section 1.409A-3(i)(5)(vii).

(e) "**Change of Control Date**" means any date after the date hereof on which a Change of Control occurs; provided, however, if a Change of Control occurs and if Executive's employment with the Company is terminated or an event constituting Good Reason (as defined below) occurs prior to the Change of Control, and if it is reasonably demonstrated by Executive that such termination or event (i) was at the request of a third party who has taken steps reasonably calculated to effect the Change of Control, or (ii) otherwise arose in connection with or in anticipation of the Change of Control then, for all purposes of this Agreement, the Change of Control Date shall mean the date immediately prior to the date of such termination or event.

(f) "**Code**" means the Internal Revenue Code of 1986, as amended, and the regulations promulgated thereunder.

(g) "**Date of Termination**" means the date specified in a Notice of Termination pursuant to Section 8 hereof, or Executive's last date as an active employee of the Company before a termination of employment due to death, Disability or other reason, as the case may be.

(h) "**Disability**" means a condition entitling Executive to benefits under the Company's long term disability plan, policy or arrangement; provided, however, if no such plan, policy or arrangement is then maintained by the Company and applicable to the Executive, "Disability" will mean a mental or physical condition that renders Executive substantially incapable of performing her duties and obligations under this Agreement, after taking into account provisions for reasonable accommodation, as determined by a medical doctor (such doctor to be mutually determined in good faith by the parties) for three or more consecutive months or for a total of six months during any 12 consecutive months.

(i) "**Effective Period**" means the period beginning on the Change of Control Date and ending 24 months after the date of the related Change of Control.

(j) "**Good Reason**" means, unless Executive has consented in writing thereto, the occurrence of any of the following: (i) the assignment to Executive of any duties materially inconsistent with Executive's position, including any change in title, authority, duties or responsibilities or any other action which results in a material diminution in such, title, authority, duties or responsibilities; (ii) a material reduction in Executive's Base Salary by the Company other than in accordance with Section 5(a); (iii) the relocation of Executive's office to a location more than 30 miles from Warrington, Pennsylvania; (iv) a material breach of this Agreement by the Company; or (v) the failure of the Company to obtain the assumption in writing of the Company's obligation to perform this Agreement by any successor to all or substantially all of the assets of the Company within 15 days after a Business Combination or a sale or other disposition of all or substantially all of the assets of the Company.

EXHIBIT B

FORM OF PROPRIETARY INFORMATION, INVENTIONS,
NON-SOLICITATION AND NON-COMPETITION AGREEMENT

The following is an agreement ("Agreement") between **WINDTREE THERAPEUTICS, INC.**, a Delaware corporation, and any successor in interest (the "Company") and me, **DIANE CARMAN**, and this Agreement is a material part of the consideration for my employment by the Company:

1. Job Title and Responsibility: I understand my job title with the Company will be **Senior Vice President and General Counsel** and the Company may change this title at any time with my written consent. My job duties and responsibilities will be those reasonably assigned to me by the Company from time to time consistent with the position of General Counsel of a publicly-traded company.

2. Consideration. I understand the consideration to me for entering into this Agreement is my employment with the Company, my base compensation, eligibility to earn bonuses, be granted incentive equity and eligibility to receive severance benefits, and I agree this consideration is fully adequate to support this Agreement.

3. Proprietary Information. I recognize the Company is engaged in a continuous program of research, development and production. I also recognize the Company possesses or has rights to secret, private, confidential information and processes (including processes and information developed by me during my employment by the Company) which are valuable, special and unique assets of the Company and which have commercial value in the Company's business ("Proprietary Information"). By way of illustration, this Proprietary Information includes, but is not limited to, information and details regarding the Company's business, trade or business secrets, inventions, intellectual property, systems, policies, records, reports, manuals, documentation, models, data and data bases, products, processes, operating systems, manufacturing techniques, research and development techniques and processes, devices, methods, formulas, compositions, compounds, projects, developments, plans, research, financial data, personnel data, internal business information, strategic and staffing plans and practices, business, marketing, promotional or sales plans, practices or programs, training practices and programs, costs, rates and pricing structures and business methods, computer programs and software, customer and supplier identities, information and lists, confidential information regarding customers and suppliers, and contacts at or knowledge of Company suppliers and customers or of prospective or potential customers of the Company.

4. Obligation of Confidentiality. I understand and agree my employment creates a relationship of confidence and trust between the Company and me with respect to (i) all Proprietary Information, and (ii) the confidential information of others with which the Company has a business relationship. At all times, both during my employment by the Company and after the termination of my employment (whether voluntary or involuntary), I will keep in confidence and trust all such information, and I will not use, reveal, communicate, or disclose any such Proprietary Information or confidential information to anyone or any entity, without the written consent of the Company, unless I am ordered to make disclosure by a court of competent jurisdiction.

Notwithstanding the foregoing, I understand nothing in this Agreement prohibits me from initiating communications directly with, responding to any inquiries from, providing testimony before, providing confidential information to, reporting possible violations of law or regulation to, or from filing a claim or assisting with an investigation directly with a self-regulatory authority or a government agency or entity, including the U.S. Equal Employment Opportunity Commission, the Department of Labor, the National Labor Relations Board, the Department of Justice, the Securities and Exchange Commission, the Congress, and any agency Inspector General (collectively, the "Regulators"), or from making other disclosures that are protected under the whistleblower provisions of state or federal law or regulation. In connection with any such activity, I must identify any information that is confidential and ask the Regulator for confidential treatment of such information. Despite the foregoing, I am not permitted to reveal to any third party, including any governmental, law enforcement, or regulatory authority, information employee came to learn during the course of my employment with the Company that is protected from disclosure by any applicable privilege, including but not limited to the attorney-client privilege, attorney work product doctrine and/or other applicable legal privileges. The Company does not waive any applicable privileges or the right to continue to protect its privileged attorney-client information, attorney work product, and other privileged information. Notwithstanding any other provisions of this Agreement, pursuant to 18 USC Section 1833(b), I shall not be held criminally or civilly liable under any federal or state trade secret law for the disclosure of a trade secret of the Company that is made: (a) confidentially to a federal, state, or local government official, either directly or indirectly, or to an attorney, and solely for the purpose of reporting or investigating a suspected violation of law; or (b) in a complaint or other document filed in a lawsuit or other proceeding, if such filing is made under seal. If I file a lawsuit for retaliation by the Company for reporting a suspected violation of law, I may disclose a trade secret of the Company to my attorney and use the trade secret information in related court proceedings, provided I file any document containing the trade secret information under seal and does not disclose the trade secret, except pursuant to court order.

5. Ownership, Disclosure and Assignment of Proprietary Information and Inventions. In addition, I hereby agree as follows:

(a) Ownership and Assignment. All Proprietary Information is, and shall be, the sole and exclusive property of the Company and its assigns, and the Company and its assigns shall be the sole and exclusive owner of all Proprietary Information, including, but not limited to, trade secrets, inventions, patents, trademarks, copyrights, and all other rights in connection with such Proprietary Information. I agree I have no rights in such Proprietary Information. I hereby assign, and shall assign, to the Company and its assigns any and all rights, title and interest I may have or acquire in such Proprietary Information. Any copyrightable work prepared in whole or in part by me in the course of my employment shall be deemed "a work made for hire" under applicable copyright laws, and the Company and its assigns shall own all of the rights in any copyright.

(b) Return of Materials and Property. All documents, records, apparatus, equipment, data bases, data and information stored in computers or on electronic disks, and other electronic, computer, intellectual, and physical property ("Materials and Property"), whether or not pertaining to Proprietary Information, furnished to me by the Company or produced by me or others in connection with employment, shall be and remain the sole and exclusive property of the Company. I shall return to the Company all such Materials and Property as and when requested by the Company. Even if the Company does not so request, I shall return all such Materials and Property upon termination of employment by me or by the Company for any reason, and I will not take with me any such Materials or Property, or any reproduction thereof, upon such termination.

(c) Notification. During the Term of my employment and for one (1) year thereafter, I will promptly disclose to the Company, or any persons designated by it, all improvements, inventions, intellectual property, works of authorship, formulas, ideas, processes, techniques, discoveries, developments, designs, innovations, know-how and data, and creative works in which copyright and/or unregistered design rights will subsist in various media (all collectively called herein, "Inventions"), whether or not such Inventions are patentable, which I make or conceive, contribute to, reduce to practice, or learn, either alone or jointly with others.

(d) Ownership of Inventions. I agree and acknowledge all Inventions which I make, conceive, develop, or reduce to practice (in whole or in part, either alone or jointly with others) at any time during my employment by the Company, and (i) which were created using the equipment, supplies, facilities or trade secret information of the Company, or (ii) which were developed during the hours for which I was compensated by the Company, or (iii) which relate, at the time of conception, creation, development or reduction to practice, to the business of the Company or to its actual or demonstrably anticipated research and development, or (iv) which result from any work performed by me for the Company, shall be the sole and exclusive property of the Company and its assigns (and to the fullest extent permitted by law shall be deemed works made for hire), and the Company and its assigns shall be the sole and exclusive owner of all Inventions, patents, copyrights and all other rights in connection therewith. I hereby assign to the Company any and all rights I may have or acquire in such Inventions. I agree any Invention required to be disclosed under paragraph (c), above, within one (1) year after the termination of my employment shall be presumed to have been conceived or made during my employment with the Company and will be assigned to the Company unless and until I prove and establish to the contrary.

(e) Assistance and Cooperation. With respect to Inventions described in paragraph (d), above, I will assist the Company in every proper way (but at the Company's expense) to obtain, and from time to time enforce, patents, copyrights or other rights on these Inventions in any and all countries, and will execute all documents reasonably necessary or appropriate for this purpose. This obligation shall survive the termination of my employment. In the event the Company is unable for any reason whatsoever to secure my signature to any document reasonably necessary or appropriate for any of the foregoing purposes (including renewals, extensions, continuations, divisions or continuations in part), I hereby irrevocably designate and appoint the Company, and its duly authorized officers and agents, as my agents and attorneys-in-fact to act for and in my behalf and instead of me, but only for the purpose of executing and filing any such document and doing all other lawfully permitted acts to accomplish the foregoing purposes with the same legal force and effect as if executed by me.

(f) Exempt Inventions. I understand this Agreement does not require assignment of an Invention for which no equipment, supplies, facilities, resources, or trade secret information of the Company was used and which was developed entirely by me on my own time, unless the invention relates, (i) directly to the business of the Company, or (ii) to the Company's actual or demonstrably anticipated research or development. However, I will disclose to the Company any Inventions I claim are exempt, as required by paragraph (c), above, in order to permit the Company to determine such issues as may arise. Such disclosure shall be received in confidence by the Company.

6. Prior Inventions. As a matter of record, I attach hereto as Schedule 1 a complete list of all inventions or improvements relevant to the subject matter of my employment by the Company which have been made or conceived or first reduced to practice by me, alone or jointly with others, prior to my employment with the Company, I desire to remove from the operation of this Agreement, and I covenant such list is complete. If no such list is attached to this Agreement, I represent I have no such inventions and improvements at the time of my signing this Agreement.

7. Other Business Activities. So that the Company may be aware of the extent of any other demands upon my time and attention, I will disclose to the Company (such disclosure to be held in confidence by the Company) the nature and scope of any other business activity in which I am or become engaged during the term of my employment. During the term of my employment, I will not engage in any business activity or employment which is in competition with, or is related to, the Company's business or its actual or demonstrably anticipated research and development, or that will affect in any manner my ability to perform fully all of my duties and responsibilities for the Company.

8. Non-Interference and Non-Solicitation of Employees, Customers and Others. I will not now or at any time in the future, anywhere in the world, disrupt, damage, impair or interfere with the business of the Company, whether by way of interfering with or raiding its employees, disrupting its relationships with customers, agents, vendors, distributors or representatives, or otherwise. During my employment with the Company and for eighteen (18) months thereafter, I will not directly or indirectly solicit, encourage, induce or endeavor to entice away from the Company, or otherwise interfere with the relationship of the Company with, any person who is employed or engaged by the Company as an employee, consultant or independent contractor or who was so employed or engaged at any time during the six (6) months preceding the termination of my employment; provided, nothing herein shall prevent me from engaging in discussions regarding employment, or employing, any such employee, consultant or independent contractor (i) if such person shall voluntarily initiate such discussions without any such solicitation, encouragement, enticement or inducement prior thereto on my part or (ii) if such discussions shall be held as a result of, or any employment shall be the result of, the response by any such person to a written employment advertisement placed in a publication of general circulation, general solicitation conducted by executive search firms, employment agencies or other general employment services, not directed specifically at any such employee, consultant or independent contractor.

9. Non-Competition During and After Employment. During my employment with the Company or at any time within a period of one (1) year after the termination of my employment, I shall not, directly or indirectly, anywhere in the world, without the prior written consent of the Company, either as an employee, employer, consultant, agent, principal, partner, stockholder, corporate officer, director, or in any other individual or representative capacity compete with the Company in the business of developing or commercializing (i) pulmonary surfactants or any other category of compounds which form the basis of the Company's material drug products, or (ii) any material medical device products under development by the Company, including without limitation the Company's capillary aerosol generator, series of aerosol-conducting airway connectors and related componentry, and similar medical devices, in each case, as determined in good faith by the Company on the termination date of my employment. Notwithstanding the foregoing, the Company and I acknowledge and agree that I may engage in the practice of law without limitation, including, but not limited to, serving as a general and/or in-house counsel to any company, subsequent to the termination of my employment for any reason, subject to my compliance with applicable ethical requirements.

10. Obligations to Former Employers. I represent my execution of this Agreement, my employment with the Company, and my performance of my duties and proposed duties to the Company will not violate any obligations or agreements I have, or may have, with any former employer or any other third party, including any obligations and agreements requiring me not to compete or to keep confidential any proprietary or confidential information. I have not entered into, and I will not enter into, any agreement which conflicts with this Agreement or would, if performed by me, cause me to breach this Agreement. I further represent I have no knowledge of any pending or threatened litigation to which the Company may become a party by virtue of my association with the Company. I further agree to immediately inform the Company of any such pending or threatened litigation should it come to my attention during the course of my employment. I also agree I provided to the Company for its inspection before I signed this Agreement all confidentiality, non-compete, non-solicitation, and all other employment-related agreements that I am party to or which involve me, that would impact my ability to perform my obligations to the Company.

11. Confidential Information of, and Agreements with, Former Employers. In the course of performing my duties to the Company, I will not utilize any trade secrets, proprietary or confidential information of or regarding any former employer or business affiliate, nor violate any written or oral, express or implied agreement with any former employer or business affiliate.

12. United States Government Obligations. I acknowledge the Company from time to time may have agreements with other persons or with the United States Government, or agencies thereof, which impose obligations or restrictions on the Company regarding inventions made during the course of work under such agreements or regarding the confidential nature of such work. I agree to be bound by all such obligations and restrictions which are made known to me and to take all action necessary to discharge the obligations of the Company under such agreements.

13. Remedies. I acknowledge my failure to comply with, or my breach of, any of the terms and conditions of this Agreement may irreparably harm the Company, and money damages may not adequately compensate the Company for this harm. Accordingly, I acknowledge in the event of a threatened or actual breach by me of any provision of this Agreement, in addition to any other remedies the Company may have at law, the Company shall be entitled to seek equitable relief in the form of specific performance, temporary restraining order, temporary or permanent injunction or any other equitable remedy then available, without requiring the Company to post any bond. I agree nothing herein contained shall be construed as prohibiting the Company from pursuing any other remedies available to it for such threatened or actual breach, including money damages.

14. Not an Employment Agreement. I acknowledge and agree this Agreement is not a contract of employment, it should not be construed as a guarantee of my employment for any period of time, and that I am employed by the Company at will and my employment may be terminated by the Company for any lawful reason or no reason.

15. Miscellaneous.

(a) Reformation and Severability. If any provision of this Agreement is held to be invalid or unenforceable under applicable law, such provision shall be reformed and/or construed, if possible, to be enforceable under applicable law; otherwise, such provision shall be excluded from this Agreement and the balance of the Agreement shall remain fully enforceable and valid in accordance with its terms. To the extent the restrictions imposed by Sections 8 and 9 are interpreted by any court to be unreasonable in geographic and/or temporal scope, such restrictions shall be deemed automatically reduced to the extent necessary to coincide with the maximum geographic and/or temporal restrictions deemed by such court not to be unreasonable.

(b) No Waiver. No delay or omission by the Company in exercising any right hereunder will operate as a waiver of that or any other right. A waiver or consent given by the Company on any one occasion is effective only in that instance and will not be construed as a bar to or waiver of any right on any other occasion.

(c) Reassignment. I expressly consent to be bound by the provisions of this Agreement for the benefit of the Company or any subsidiary or affiliate thereof to whose employment I may be transferred, without the necessity that this Agreement be reassigned at the time of such transfer.

(d) Applicable Law. This Agreement shall be governed by and construed in accordance with the laws of the Commonwealth of Pennsylvania (but not the law or principles of conflict of laws), and the parties submit to the jurisdiction of the courts of Pennsylvania.

(e) Effective Date. This Agreement shall be effective as of the first day of my employment by the Company, shall be binding upon me, my heirs, executors, assigns and administrators, and shall inure to the benefit of the Company, its successors and assigns.

(f) Entire Agreement. This Agreement contains the entire agreement of the parties relating to the subject matter herein, and may not be waived, changed, extended or discharged except by an agreement in writing signed by both parties.

I acknowledge and agree I have fully read and understand all of the terms and provisions of this Agreement, I have had the opportunity to consult with an attorney and to discuss this Agreement with an attorney, I have had any questions regarding the effect of this Agreement or the meaning of its terms answered to my satisfaction, and, intending to be legally bound hereby, I freely and voluntarily sign this Agreement.

Accepted and Agreed to:

By: /s/ Diane Carman
Name: Diane Carman
Date:
SS#: x9360

WINDTREE THERAPEUTICS, INC.

By: /s/ Craig E. Fraser
Name: Craig E. Fraser
Title: President and CEO
Date:

SCHEDULE 1

Windtree Therapeutics, Inc.
2600 Kelly Road, Suite 100
Warrington, PA 18976

Attn: Craig E. Fraser

1. The following is a complete list of all inventions or improvements relevant to the subject matter of my employment by Windtree Therapeutics, Inc. (the "Company") that have been made or conceived or first reduced to practice by me, alone or jointly with others, prior to my employment by the Company I desire to remove from the operation of the Company's Proprietary Information and Inventions and Non-Solicitation Agreement.

__X__ No inventions or improvements.

_____ See below. Any and all inventions regarding

_____ Additional sheets attached.

2. I propose to bring to my employment the following materials and documents of a former employer:

__X__ No materials or documents.

_____ See below.

_____
Diane Carman

_____
Date

Exhibit 23.1

Consent of Independent Registered Public Accounting Firm

We consent to the incorporation by reference in the following Registration Statements:

1. Registration Statement (Form S-1 No. 333-217161, Form S-1 No. 333-231128, Form S-1 No. 333-235977, and Form S-1 333-236085) of Windtree Therapeutics, Inc. and in related Prospectuses,

2. Registration Statement (Form S-3 No. 333-248874) of Windtree Therapeutics, Inc. and in related Prospectuses,

3. Registration Statement (Form S-3 No. 333-261878) of Windtree Therapeutics, Inc. and in related Prospectuses;

4. Registration Statement (Form S-8 No. 333-180497, Form S-8 No. 333-184277, Form S-8 No. 333-189966, Form S-8 No. 333-197139, Form S-8 No. 333-209141, Form S-8 No. 333-224338, and Form S-8 No. 333-230907) pertaining to the Windtree Therapeutics, Inc. 2011 Long-Term Incentive Plan,

5. Registration Statement (Form S-8 No. 333-148028) pertaining to the Windtree Therapeutics, Inc. 2007 Long-Term Incentive Plan,

6. Registration Statement (Form S-8 No. 333-33900, Form S-8 No. 333-55900, Form S-8 No. 333-67422, Form S-8 No. 333-100824, Form S-8 No. 333-109274, Form S-8 No. 333-116268, Form S-8 No. 333-127790, Form S-8 No. 333-138476, Form S-8 No. 333-208879, Form S-8 No. 333-209141 and Form S-8 No. 210464) pertaining to the Amended and Restated 1998 Stock Incentive Plan of Windtree Therapeutics, Inc.,

7. Registration Statement (Form S-8 No. 333-59945) pertaining to the Amended and Restated 1998 Stock Incentive Plan of Windtree Therapeutics, Inc., the 1996 Stock Option/Stock Issuance Plan of Windtree Therapeutics, Inc., and the 1996 Stock Option/ Stock Issuance Plan of Acute Therapeutics, Inc.,

8. Registration Statement (Form S-8 No. 333-110412, Form S-8 No. 333-137643, Form S-8 No. 333-156443, Form S-8 No. 333-164470, Form S-8 No. 333-165809, Form S-8 No. 333-169662, Form S-8 No. 333-173259, Form S-8 No.333-180497, Form S-8 No. 333-187486, Form S-8 No. 333-191502, Form S-8 No. 333-197139, Form S-8 No. 333-201478, Form S-8 No. 333-208879, and S-8 No. 333-209141) pertaining to the 401(k) Plan of Windtree Therapeutics, Inc.,

9. Registration Statement (Form S-8 No. 333-253065) pertaining to the Windtree Therapeutics, Inc. 2020 Equity Incentive Plan, and

10. Registration Statement (Form S-8 No. 333-253067) pertaining to certain Non-Qualified Stock Option Inducement Awards;

of our report dated March 31, 2022, with respect to the consolidated financial statements of Windtree Therapeutics, Inc. and subsidiaries included in this Annual Report (Form 10-K) of Windtree Therapeutics, Inc. and subsidiaries for the year ended December 31, 2021.

/s/ Ernst & Young LLP

Philadelphia, Pennsylvania
March 31, 2022

Exhibit 31.1

CERTIFICATION

I, Craig E. Fraser, certify that:

1. I have reviewed this Annual Report on Form 10-K of Windtree Therapeutics, Inc.;

2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;

3. Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this report;

4. The registrant's other certifying officers and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reports (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f) for the registrant and have:

    (a) designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;

    (b) designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;

    (c) evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and

    (d) disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and

5. The registrant's other certifying officers and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of the registrant's board of directors (or persons performing the equivalent function):

    (a) all significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and

    (b) any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Date: March 31, 2022

/s/ Craig E. Fraser
Craig E. Fraser
President and Chief Executive Officer
(Principal Executive Officer)

Exhibit 31.2

CERTIFICATION

I, John P. Hamill, certify that:

1. I have reviewed this Annual Report on Form 10-K of Windtree Therapeutics, Inc.;

2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;

3. Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this report;

4. The registrant's other certifying officers and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:

    (a) designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;

    (b) designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;

    (c) evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and

    (d) disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and

5. The registrant's other certifying officers and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of the registrant's board of directors (or persons performing the equivalent function):

    (a) all significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and

    (b) any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Date: March 31, 2022

/s/ John P. Hamill
John P. Hamill
Senior Vice President and Chief Financial Officer
(Principal Financial Officer)

Exhibit 32.1

CERTIFICATION PURSUANT TO
18 U.S.C. SECTION 1350,
AS ADOPTED PURSUANT TO
SECTION 906 OF THE SARBANES-OXLEY ACT OF 2002

In connection with the Annual Report of Windtree Therapeutics, Inc. (the "Company") on Form 10-K for the year ended December 31, 2021, as filed with the Securities and Exchange Commission on the date hereof (the "Report"), each of the undersigned officers of the Company certifies, pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002, that to such officer's knowledge:

(1) The Report fully complies with the requirements of Section 13(a) or 15(d) of the Securities Exchange Act of 1934; and

(2) The information contained in the Report fairly presents, in all material respects, the financial condition and results of operations of the Company.

Date: March 31, 2022

/s/ Craig E. Fraser
Craig E. Fraser
President and Chief Executive Officer
(Principal Executive Officer)

/s/ John P. Hamill
John P. Hamill
Senior Vice President and Chief Financial Officer
(Principal Financial Officer)