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UNITED STATES
SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

FORM 10-K

(Mark One)

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

For the fiscal year ended December 31, 2020.

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 001-38899

Milestone Pharmaceuticals Inc.

(Exact name of registrant as specified in its charter)

Quebec	**Not applicable**
(State or Other Jurisdiction of Incorporation or Organization)	(I.R.S. Employer Identification No.)
1111 Dr. Frederik-Phillips Boulevard, Suite 420 Montréal, Québec CA	**H4M 2X6**
(Address of Principal Executive Offices)	(Zip Code)

Registrant's telephone number, including area code **(514)-336-0444**

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

Title of each class	**Trading Symbol(s)**	**Name of each exchange on which registered**
Common Shares	MIST	The Nasdaq Stock Market LLC

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 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, if any, every Interactive Data File required to be submitted pursuant to Rule 405 of Regulation S-T during the preceding 12 months (or for such shorter period that the registrant was required to submit and post such files). Yes ☒ No ☐

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, a 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. Yes ☐ No ☒

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

The aggregate market value (approximate) of the registrant's common equity held by non-affiliates based on the closing price of a share of the registrant's common share for The Nasdaq Stock Market on June 30, 2020 (the last business day of the registrant's most recently completed second fiscal quarter) was $ 93.3 million.

As of March 5, 2021, the total number of shares outstanding of the registrant's Common Shares was 29,846,000 shares, net of treasury shares.

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This Annual Report on Form 10-K contains references to United States dollars and Canadian dollars. All dollar amounts referenced, unless otherwise indicated, are expressed in United States dollars. References to “$” are to United States dollars and references to “C$” are to Canadian dollars.

SPECIAL NOTE REGARDING FORWARD-LOOKING STATEMENTS

This Annual Report on Form 10-K contains forward-looking statements about us and our industry that involve substantial risks and uncertainties. All statements other than statements of historical facts contained in this Annual Report on Form 10-K, including statements regarding our strategy, future financial condition, future operations, projected costs, prospects, plans, objectives of management and expected market growth, are forward-looking statements. In some cases, you can identify forward-looking statements by terminology such as "aim," "anticipate," "assume," "believe," "contemplate," "continue," "could," "design," "due," "estimate," "expect," "goal," "intend," "may," "objective," "plan," "predict," "positioned," "potential," "seek," "should," "target," "will," "would" and other similar expressions that are predictions of or indicate future events and future trends, or the negative of these terms or other comparable terminology.

We have based these forward-looking statements largely on our current expectations and projections about future events and financial trends that we believe may affect our financial condition, results of operations, business strategy and financial needs. These forward-looking statements are subject to a number of known and unknown risks, uncertainties and assumptions, including risks described in the section titled "Risk Factors" and elsewhere in this Annual Report on Form 10-K, regarding, among other things:

- the initiation, timing, progress and results of our current and future clinical trials of etripamil, including our Phase 3 clinical trials of etripamil for the treatment of paroxysmal supraventricular tachycardia, our Phase 2 clinical trial of etripamil for the treatment of atrial fibrillation and rapid ventricular rate, and of our research and development programs;
- uncertain impacts that the COVID-19 pandemic may have on our business, strategy, clinical trial progress and research and development efforts;
- our plans to develop and commercialize etripamil and any future product candidates;
- our estimates regarding expenses, future revenue, capital requirements and needs for additional financing;
- our ability to successfully acquire or in-license additional product candidates on reasonable terms;
- our ability to establish collaborations or obtain additional funding;
- our ability to obtain regulatory approval of our current and future product candidates;
- our expectations regarding the potential market size and the rate and degree of market acceptance of etripamil and any future product candidates;
- our ability to fund our working capital requirements and expectations regarding the sufficiency of our capital resources;

- the implementation of our business model and strategic plans for our business, etripamil and any future product candidates;
- our intellectual property position and the duration of our patent rights;
- developments or disputes concerning our intellectual property or other proprietary rights;
- our expectations regarding government and third-party payor coverage and reimbursement;
- our ability to compete in the markets we serve;
- the impact of government laws and regulations;
- developments relating to our competitors and our industry; and
- the factors that may impact our financial results.

The foregoing list of risks is not exhaustive. Other sections of this Annual Report on Form 10-K may include additional factors that could harm our business and financial performance. Moreover, we operate in a very competitive and rapidly changing environment. New risk factors emerge from time to time, and it is not possible for our management to predict all risk factors nor can we assess the impact of all factors on our business or the extent to which any factor, or combination of factors, may cause actual results to differ materially from those contained in, or implied by, any forward-looking statements.

In light of the significant uncertainties in these forward-looking statements, you should not rely upon forward-looking statements as predictions of future events. Although we believe that we have a reasonable basis for each forward-looking statement contained in this Annual Report on Form 10-K, we cannot guarantee that the future results, levels of activity, performance or events and circumstances reflected in the forward-looking statements will be achieved or occur at all. You should refer to the section titled "Risk Factors" for a discussion of important factors that may cause our actual results to differ materially from those expressed or implied by our forward-looking statements. Furthermore, if our forward-looking statements prove to be inaccurate, the inaccuracy may be material. Except as required by law, we undertake no obligation to publicly update any forward-looking statements, whether as a result of new information, future events or otherwise. The Private Securities Litigation Reform Act of 1995 and Section 27A of the Securities Act of 1933, as amended, do not protect any forward-looking statements that we make in connection with this Annual Report on Form 10-K.

SUMMARY OF RISK FACTORS

Our business is subject to numerous risks and uncertainties, including those described in Item 1A "*Risk Factors*". These risks include, but are not limited to the following:

- We have incurred significant operating losses since inception and anticipate that we will continue to incur substantial operating losses for the foreseeable future and may never achieve or maintain profitability.
- We will require substantial additional funding to finance our operations. If we are unable to raise capital when needed, we could be forced to delay, reduce or terminate our development of etripamil or other operations.
- Raising additional capital may cause dilution to our shareholders, restrict our operations or require us to relinquish rights to our product candidates.
- We have only one product candidate, etripamil, for which we are currently pursuing clinical development. Our future success is substantially dependent on the successful clinical development and regulatory approval of etripamil. If we are not able to obtain required regulatory approvals for etripamil or any future product candidates, we will not be able to commercialize etripamil or any future product candidates and our ability to generate revenue will be adversely affected.
- We may not be successful in our efforts to expand our pipeline of product candidates beyond etripamil for PSVT.
- The development of additional product candidates is risky and uncertain.
- Success in preclinical studies or earlier clinical trials may not be indicative of results in future clinical trials and we cannot assure you that any ongoing, planned or future clinical trials will lead to results sufficient for the necessary regulatory approvals.
- Our business, operations and clinical development timelines and plans have been adversely affected by the effects of health epidemics, including the COVID-19 pandemic, and could be affected by future health epidemics.
- We may encounter substantial delays or difficulties in our clinical trials.
- Enrollment and retention of patients in clinical trials is an expensive and time-consuming process and could be delayed, made more difficult or rendered impossible by multiple factors outside our control.
- If we are unable to establish sales and marketing capabilities or enter into agreements with third parties to market and sell etripamil or any future product candidates, we may not be successful in commercializing etripamil or any future product candidates, if and when they are approved.
- Even if etripamil or any future product candidates receive marketing approval, they may fail to achieve market acceptance by physicians, patients, third-party payors or others in the medical community necessary for commercial success.
- Even if we successfully obtain approval for etripamil, its success will be dependent on its proper use.
- If the market opportunities for etripamil and any future product candidates are smaller than we estimate, our business may suffer.
- Coverage and adequate reimbursement may not be available for etripamil or any future product candidates, which could make it difficult for us to gain market acceptance.
- Even if we obtain and maintain approval for etripamil or any future product candidates from the FDA, we may never obtain approval of etripamil or any future product candidates outside of the United States, which would limit our market opportunities and could harm our business.
- Even if we obtain regulatory approval for etripamil or any future product candidates, they will remain subject to ongoing regulatory oversight.
- We will rely on third parties to produce clinical and commercial supplies of etripamil and any future product candidates.
- We rely on third parties to conduct, supervise and monitor our preclinical studies and clinical trials, and if those third parties perform in an unsatisfactory manner, it may harm our business.
- Etripamil is intended to be used with a nasal-spray device, which may result in additional regulatory and supply risks.

- If we are unable to obtain and maintain patent protection for etripamil or any future product candidates, or if the scope of the patent protection obtained is not sufficiently broad, our competitors could develop and commercialize drugs similar or identical to ours, and our ability to commercialize successfully our product candidates may be impaired.
- Our future success depends on our ability to retain key executives and to attract, retain and motivate qualified personnel.
- The market price of our common shares has been and may continue to be volatile and fluctuate substantially, and you could lose all or part of your investment.
- Our common shares are thinly traded and our shareholders may be unable to sell their shares quickly or at market price.
- Concentration of ownership of our common shares among our existing executive officers, directors and principal shareholders may prevent new investors from influencing significant corporate decisions.

PART I

ITEM 1. BUSINESS

Company Overview

We are a biopharmaceutical company focused on the development and commercialization of innovative cardiovascular medicines. Our lead product candidate etripamil is a novel, potent and short-acting calcium channel blocker that we designed as a rapid-onset nasal spray to be self-administered by patients. We are developing etripamil to treat paroxysmal supraventricular tachycardia, or PSVT, atrial fibrillation (AF) and rapid ventricular rate, or AFib-RVR, and other cardiovascular indications.

PSVT is a rapid heart rate condition characterized by episodes of supraventricular tachycardia, or SVT, that start and stop without warning. Episodes of SVT are often experienced by patients with symptoms including palpitations, sweating, chest pressure or pain, shortness of breath, sudden onset of fatigue, lightheadedness or dizziness, fainting and anxiety. Calcium channel blockers have long been approved for the treatment of PSVT as well as other cardiac conditions. Calcium channel blockers available in oral form are frequently used prophylactically to control the frequency and duration of future episodes of SVT. For treatment of episodes of SVT, approved calcium channel blockers are administered intravenously under medical supervision, usually in the emergency department. The combination of convenient nasal-spray delivery, rapid-onset and short duration of action of etripamil has the potential to shift the current treatment paradigm for episodes of SVT away from the burdensome and costly emergency department setting. If approved, we believe that etripamil will be the first self-administered therapy for the rapid termination of episodes of SVT wherever and whenever they occur.

In March 2020, we reported topline results of the first part of the NODE-301 pivotal trial of etripamil for the treatment of PSVT, which is a placebo-controlled Phase 3 safety and efficacy trial. The first part of NODE-301, which enrolled a total of 431 patients across 65 sites in the United States and Canada, did not meet its primary endpoint of time to conversion of SVT to sinus rhythm compared to placebo over the five-hour period after study drug administration. The median time to conversion for etripamil was 25 minutes (95% CI: 16, 43) compared to 50 minutes (95% CI: 31,101) for placebo (p=0.12). Despite early activity, including the conversion of 61% of etripamil patients compared to 45% of placebo patients within 45 minutes after study drug administration (p=0.02), a time period consistent with etripamil's pharmacological activity, results from the latter part of the analysis confounded the statistical analysis of the primary endpoint.

The study demonstrated statistically significant differences in favor of etripamil treated patient compared to those taking placebo in the secondary endpoint of patient reported treatment satisfaction, as measured by a treatment satisfaction questionnaire for medication (TSQM-9), including global satisfaction (p=0.0069) and effectiveness scores (p=0.0015). Additionally, there was a trend towards improvement in the percentage of patients seeking rescue medical intervention,

including in the emergency department, with 15% and 27% etripamil and placebo patients, respectively, reporting such intervention (p=0.12).

The most common AEs observed in patients receiving etripamil were nasal irritation (19.6%) and congestion (6.7%), and these events were typically transient in nature and most commonly characterized by patients as mild in severity. There were no significant differences in incidences of severe adverse events or adverse events of interest, such as atrioventricular nodal blocks or blood pressure-related symptoms, across the etripamil and placebo groups. We believe the safety and tolerability data from the first part of the NODE-301 trial is supportive of at-home use of etripamil, with adverse events, or AEs, largely consistent with those observed in prior trials.

We are continuing the second part of the NODE-301 trial, NODE-301B, which we have renamed the RAPID trial. The RAPID trial continues to follow patients already randomized in the NODE-301 trial who did not administer a dose of the study drug before the end of the first part of the trial. We are also expanding the RAPID trial to add more clinical study sites and more patients. We plan to analyze the final data from the RAPID trial separately as a second efficacy data set.

In July 2020, we announced that we received guidance from the U.S. Food and Drug Administration, or FDA, on our proposal to alter the size and design of the RAPID trial as well as the overall program based on the data from the NODE-301 trial. The FDA indicated that two studies, the RAPID study and the completed NODE-301 study, could potentially fulfill the efficacy requirement for our planned NDA for etripamil in patients with PSVT.

Under an updated statistical analysis plan, or SAP, the primary efficacy endpoint for both the RAPID and NODE-301 studies will be defined as time to conversion over the first 30 minutes, with a target p- value of less than 0.05 for each study. This endpoint supports the desire of patients to rapidly address their PSVT symptoms during an episode and ideally avoid visiting the emergency department. Later and earlier time points will also be assessed as part of secondary analyses to fully characterize the efficacy profile of etripamil.

When employing the updated SAP retrospectively to the NODE-301 data, 54% of etripamil patients vs. 35% of placebo patients converted within 30 minutes (HR 1.87, p=0.02). We believe, based on interactions with PSVT treating physicians and cardiovascular thought leaders, that a 50% conversion rate within 60 minutes is a clinically meaningful outcome given the symptomatic nature of SVT episodes and the lack of approved at-home treatments. Assuming a positive outcome in the RAPID study, these data could potentially serve to fulfill the efficacy requirement for the NDA.

The RAPID trial was originally an ongoing trial named NODE-301B and was designed to collect double-blind data from randomized patients who had not yet experienced an SVT event after the NODE-301 study reached its target number of adjudicated SVT events. After receiving guidance from the FDA on our Phase 3 program, we have amended and expanded NODE-301B and renamed it the RAPID trial. The RAPID trial will include the 170 patients who are already enrolled in NODE-301B and is expected to enroll approximately 500 patients in total. The trial will be completed after a total of 180 confirmed SVT events are reached. Additional patients enrolled in the RAPID study will be randomized 1:1.

During the fourth quarter of 2020, we observed delays in our enrollment and clinical trial site startups for the RAPID study. We believe the effects of the COVID-19 pandemic and its impact contributed to such delays. As a result we have taken measures to increase the enrollment of patients by increasing the number of clinical trial sites, including more clinical sites planned in European countries to diversify and better protect the study recruitment against COVID's geographical resurgences. We are also increasing site specific support for clinical trial sites currently open. We will continue to monitor the impact of COVID-19 on the study and expect to continue these enrollment enhancing initiatives throughout 2021. While we monitor the effect of those initiatives, we are maintaining our guidance of achieving topline data from the RAPID trial in late 2021 or early 2022.

Based on discussions with the FDA regarding maximizing the treatment effect of etripamil, the RAPID study will allow for a repeat administration of study drug (either 70 mg of etripamil or placebo) for patients who have not experienced symptom relief within 10 minutes of the first study drug administration. This tailored regimen, using a repeat-dose is similar to current PSVT treatment practices with intravenous drugs in the emergency department setting. It is enabled by

the favorable safety data from the NODE-301 study. We expect that the repeat administration could benefit a broader group of patients, including those with more persistent episodes. In the NODE-301 study, 32% of etripamil patients and 14% of placebo patients converted to sinus rhythm within 10 minutes. The FDA agreed that the single and repeat administrations of etripamil could be pooled and compared to placebo for the primary analysis, resulting in no increase in the sample size.

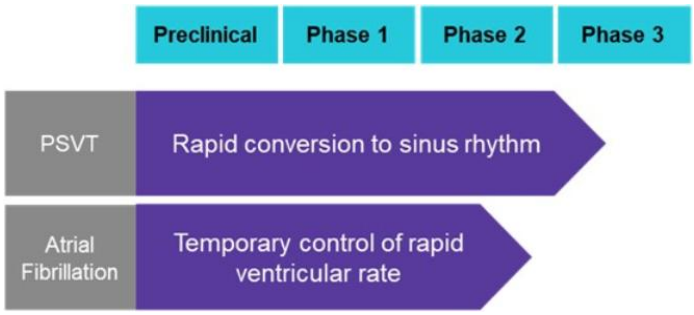
We are in the process of initiating patient access programs that have as their primary objective providing further access to etripamil for future SVT episodes to patients who have participated in the clinical development registration trials. These programs will be tailored to meet the regulatory requirements in the territories in which the clinical sites are located.

As with PSVT, calcium channel blockers are also approved for use in intravenous form for the treatment of some episodes of atrial fibrillation, or AF, in which patients experience rapid ventricular rates. Our initial qualitative market research indicates that the target addressable market for etripamil in patients with atrial fibrillation and rapid ventricular rate is approximately 40% of the five to six million patients diagnosed with atrial fibrillation. We believe that etripamil has the potential to be developed such that it can be used by patients to rapidly reduce their heart rate in the at-home setting to provide a supplemental option to the oral rate or rhythm control strategy their physician has already prescribed. We began enrollment of patients in a Phase 2 proof-of-concept clinical trial titled ReVeRA in the first quarter of 2021 to evaluate the potential effectiveness of etripamil to reduce ventricular rate in AFib-RVR episodes. The Phase 2 double blind, placebo controlled, proof-of-concept, which will be conducted in Canada in collaboration with the Montreal Heart Institute and other research centers, is expected to enroll approximately 50 patients randomized 1:1 to receive either 70 mg of etripamil nasal spray or placebo. The primary endpoint will assess reduction in ventricular rate, with key secondary endpoints including the time to achieve the maximum reduction in rate and the duration of the effect. The trial is to be conducted in the hospital or emergency department setting under medical supervision.We anticipate reporting data following disclosure of top line results of the RAPID trial.

As we generate more data on the safety and efficacy profile of etripamil in PSVT and assess the proof-of-concept results from the ReVeRA trial, we will continue to assess whether etripamil could be further developed in PSVT and AFib-RVR, and other areas of unmet medical need.

Our Pipeline

The following table sets forth the status and initial focus of etripamil.



Safety Studies

In addition to NODE-301 and the RAPID trial, the clinical development program for etripamil for PSVT consists of two other Phase 3 clinical trials, as well as completed Phase 2 and Phase 1 trials. NODE-302 is our ongoing Phase 3 open-label safety extension of the NODE-301 trial. Patients who completed NODE-301 could have enrolled in NODE-302 and received up to an additional 11 doses of etripamil. NODE-302 is a multi- center, open label study designed to evaluate the safety of etripamil nasal spray when self-administered by patients without medical supervision for spontaneous episodes of SVT in an outpatient setting. Eligibility was also contingent on satisfying all inclusion and exclusion criteria, including not experiencing a severe adverse event related to the study drug or the study procedure that precludes the self-administration of etripamil. We completed NODE-302 in late 2020 with a data set of 245 episodes with 105 patients dosed at least once out of 169 patients enrolled. Trial safety results will contribute to the etripamil safety database, and are expected to be available in 2021.

NODE-303 is a Phase 3, multi-center, open-label safety trial, evaluating the safety of etripamil when self-administered without medical supervision, and evaluating the treatment safety and efficacy of etripamil on multiple SVT episodes. We originally designed this trial to enroll enough patients to collect data on up to 1,000 patients taking etripamil in an at-home setting. With the expanded size of the RAPID trial, we expect the size of the NODE-303 study to be reduced. We expect to determine a more accurate sizing of the trial following future discussions with the FDA and other regulatory authorities. Based on a review of the NODE-301 safety data available in June 2019, the FDA and multiple European and Latin American regulatory authorities agreed to allow patient enrollment in NODE-303 without an in-office safety test dose, which is required in the RAPID trial, and in a broad patient population including patients taking concomitant beta-blockers and calcium channel blockers.

We are in the process of initiating patient access programs that have as their primary objective providing further access to etripamil to patients who have participated in the clinical development registration trials to treat future SVT episodes. These programs will be tailored to meet the regulatory requirements in the territories in which the clinical sites are located.

Phase 1 and Phase 2 Trials

We completed our Phase 2 clinical trial of etripamil for the treatment of PSVT in the United States and Canada in the electrophysiology lab, with results published in the Journal of the American College of Cardiology. Investigators reported an 87% termination rate of induced episodes of SVT within 15 minutes at the dose selected for our Phase 3 trials versus a 35% termination rate for placebo.

We have completed two Phase 1 clinical trials in healthy volunteers, characterizing the pharmacokinetics (PK) and pharmacodynamic (PD) effect of etripamil. Our most recent Phase 1 trial (NODE-102) demonstrated no significant differences in etripamil plasma levels or pharmacodynamic outcomes between Caucasian volunteers and subjects of Japanese descent, which was the primary objective of the study. In secondary analyses of all patients, the study showed that the relevant pharmacodynamic effect of 70 mg etripamil for PSVT, as measured by PR interval prolongation, is approximately in the range of 5 to 50 minutes. This period of time is consistent with data on time to conversion of SVT observed in NODE-301. When interpreting an electrocardiogram, the interval between the P wave and the R wave, known as the PR interval, is a measure of conduction over the AV node.

Our Strategy

Our goal is to identify, develop and commercialize innovative cardiovascular medicines, including etripamil for the treatment of PSVT, AFib-RVR and other cardiovascular indications, and additional clinical stage compounds for other cardiovascular conditions. The key elements of our business strategy to achieve this goal include the following:

- ***Successfully complete development and obtain regulatory approval of etripamil for the treatment of PSVT.*** We are focused on efficiently developing and obtaining approval for etripamil to treat patients with PSVT. We are maintaining our guidance of achieving topline data from the RAPID trial in late 2021 or

early 2022. We intend to first seek regulatory approval in the United States, followed by Europe and other major markets.

- ***Expand the scope of cardiovascular indications for etripamil beyond PSVT.*** We are investigating the use of etripamil for the treatment of patients with AFib-RVR. We believe that etripamil could benefit patients with AFib-RVR based on the approved use of intravenous, or IV, calcium channel blockers in this indication. We began enrollment of our Phase 2 proof-of-concept clinical trial in patients with AFib-RVR in the first quarter of 2021 . We are also exploring the additional cardiovascular opportunities for the use of etripamil.

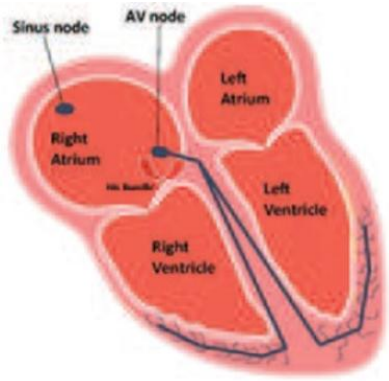
- ***Maximize the value of our programs by maintaining flexibility to commercialize our product candidates independently or through collaborative partnerships.*** We currently have exclusive development and commercialization rights for etripamil for our initial indications of PSVT and AFib-RVR. We plan to establish commercialization and marketing capabilities using a direct sales force to commercialize etripamil in the United States. Outside of the United States, we are considering commercialization strategies that may include collaborations with other companies.

- ***Leverage our expertise and experience to expand our pipeline of product candidates.*** We seek to maximize our commercial opportunities by acquiring or in-licensing product candidates for indications with significant unmet need with a focus on novel treatments for cardiovascular conditions. Our leadership team has extensive experience in developing and commercializing successful drugs. We intend to leverage the collective talent within our organization and our network to guide our development plans and pipeline expansion.

Cardiac Conduction

Normal Conduction

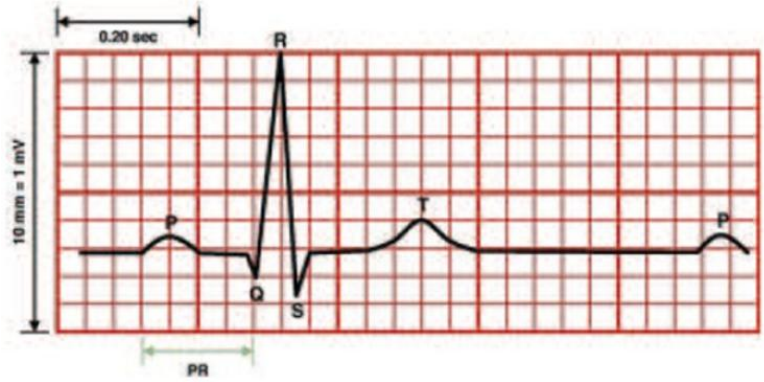
Within the right atrium, one of the heart's upper chambers, sits a specialized structure called the sinus node. The sinus node generates its own electrical signal, which spreads throughout both atria and is transmitted down to the lower chambers, the ventricles, and over another piece of electrical tissue called the atrio-ventricular, or AV, node, which is shown in the figure below. Once the signal reaches the ventricles, it causes them to contract, pumping blood out to the body. Another heartbeat does not occur until a new signal is generated from the sinus node and the cycle repeats. Under normal conditions, passage from the sinus node over the AV node is the only way for the electrical impulse to travel from the atria down to the ventricles.



The electrical signal of each heartbeat can be detected by placing sensors known as electrodes over the skin, and recorded over time in a tracing known as an electrocardiogram, or ECG. The ECG measures signal voltage and duration. To the trained interpreter, an ECG conveys a large amount of information about the structure and function of the heart, including among other things, heart rate and rhythm. Under normal physiologic conditions, an ECG has a characteristic pattern of waves corresponding to the electrical activity, contraction and relaxation of each heart chamber. This normal functioning is referred to as sinus rhythm and occurs at a heart rate of between 60 and 100 beats per minute at regular intervals.

As seen in the figure below, the various waves of an ECG tracing corresponding to the events of a single heartbeat are named with the letters P, Q, R, S and T. The interval between the P wave and the R wave, known as the PR interval, is a measure of conduction over the AV node. A normal PR interval is 0.12-0.20 seconds in duration.

ECG Tracing Graph – Event Single Heartbeat



Arrhythmias

A disruption in the heart's normal rate or rhythm is called an arrhythmia. With an arrhythmia, the heart can beat too quickly, too slowly or with an irregular pattern. A faster than normal heat rate is called tachycardia; a slower than normal heart rate is called bradycardia. Symptoms of an arrhythmia can include palpitations, lightheadedness or dizziness, chest pain, shortness of breath or sweating. PSVT and atrial fibrillation are two of the most commonly occurring arrhythmias. While PSVT is characterized by a faster than normal heart rate where the heart beats at regular intervals, with AFib-RVR the heart often beats faster than normal and always with a random, irregular rhythm. Pharmacologic treatment of PSVT focuses on terminating the arrhythmia using an agent to slow conduction over the AV node. With AFib-RVR, there are two approaches to treatment: rate control to reduce the heart rate and rhythm control to restore sinus rhythm and prevent AF recurrences.

Etripamil

We designed and are developing etripamil, a novel, potent, rapid-onset and short-acting calcium channel blocker, as a nasal spray to be administered by the patient to terminate episodes of transient cardiovascular conditions as they occur. Short pharmacological action is sufficient to resolve an episode of SVT. Accordingly, long-lasting drugs that remain in the body at significant concentrations long after the episode is resolved subject patients to unnecessary risk, given the potential for prolonged adverse events. Currently, we are in Phase 3 development for PSVT. We are also developing etripamil to provide rapid rate control for patients with acute symptomatic episodes of atrial fibrillation and are exploring other therapeutic applications where a rapid-onset and short acting non-dihydropyridine calcium channel blocking agent could provide patient benefit.

In our effort to develop potential therapies, we sought to create new chemical entities as analogs of known molecular classes with clinically validated mechanisms of action. Our goal was to preserve the beneficial pharmacology of existing molecules while altering their pharmacokinetic profile with focused medicinal chemistry to produce drugs that are fast acting and rapidly inactivated. As a result, we created a series of novel non-dihydropyridine L type calcium channel blockers containing chemical ester moieties that preserved the desired pharmacology on the heart but that could be rapidly metabolized and inactivated in the blood by serum esterases. Etripamil resulted from this effort as a new chemical entity with a short relevant pharmacodynamic effect for up to 50 minutes in humans, compared with other calcium channel blockers that have pharmacodynamic effects of several hours.

We believe that the following attributes of etripamil make it a better treatment candidate for certain episodic cardiovascular conditions than current standards of care:

- Action: Etripamil is designed to act upon the desired target for only up to 50 minutes, with the goal of reducing long-term side effects that may occur with chronic drug therapy.
- Absorption: Etripamil is designed to be absorbed into the bloodstream in less than 10 minutes through the inner lining of the nose.
- Administration: Etripamil is designed to be self-administered by patients via a nasal spray device.

To better understand the opportunity for etripamil in the United States and Europe, we have commissioned multiple market research studies. In 2017, we commissioned a study that involved qualitative in-depth interviews with 121 cardiologists, electrophysiologists, emergency medicine physicians, primary care physicians, PSVT patients and private and public payors in the United States, Germany, France, United Kingdom, Italy and Spain. In this research, cardiologists in the United States were exposed to a target product profile, or TPP, of etripamil based on our Phase 2 trial results and reported that they would use etripamil in 3.5 times as many PSVT patients as those receiving a catheter ablation, which they report as 10% of their PSVT patients. From the same research, PSVT patients in the United States reported going to the emergency department for approximately 10% of their SVT episodes and anticipated being able to avoid 50% to 75% of these emergency department visits per year by using etripamil. Furthermore, a majority of patients in this research expressed positive expectations for treatment with the etripamil TPP, including that it would provide peace of mind between episodes and a sense of control over the disease, by reducing anxiety in anticipation of future episodes and allowing them to perform activities that they perceived to be limited without a reliable at-home therapy. A minority of patients expressed negative expectations for the etripamil TPP, primarily as a result of an aversion to administering medications intranasally. When presented with hypothetical prices to the patient in the range of $30 to $60 per dose, PSVT patients in this market research also reported a desire to use etripamil for an average of approximately 50% of their SVT episodes.

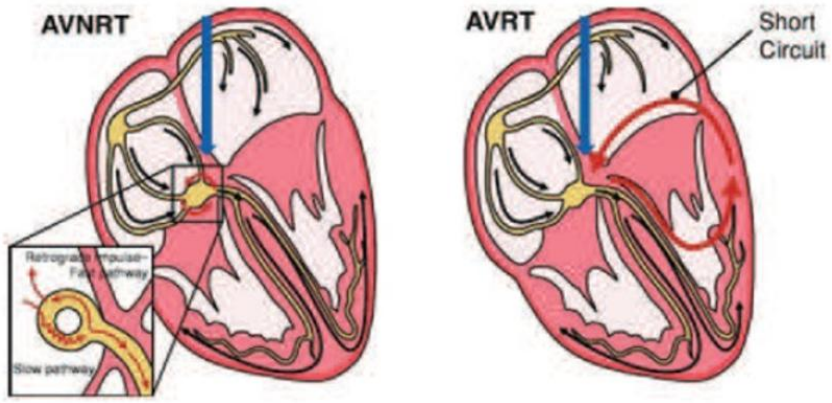
We commissioned additional market research that was conducted in 2020 after the results of NODE-301 were disclosed with 15 cardiology opinion leaders and 65 clinical cardiologists and electrophysiologists. Sixty of these physicians agreed or strongly agreed that the results of NODE-301 were clinically meaningful. We believe these responses emphasize the need for an efficacious self-administered therapy to reduce ED visits. These same physicians also responded favorably to a target product profile that included a repeat administration of etripamil, such as is being studied in the RAPID trial, with a hypothetical increase in conversion to sinus rhythm at 45 minutes from 60% to 75%, assuming a tolerability profile consistent with the NODE-301 trial.

We also commissioned market research that was conducted in 2019 with representatives of 20 regional and national commercial/medicare payors and pharmacy benefits managers, or PBMs. In this research, we asked these representatives to evaluate their receptivity to a product profile of etripamil, which assumes a single dose administration and a hypothetical profile of 70% conversion within 30 minutes for etripamil vs 30% for placebo. When presented with a range of hypothetical wholesale acquisition costs to the payors and then asked about the likelihood of coverage of etripamil by commercial and medicare payors if it was approved for PSVT, the representatives on average believed etripamil was highly likely to receive broad reimbursement by both commercial and medicare payors if net pricing was

below the specialty tier pricing threshold for government managed plans, which at the time of the survey was $670 per month.

PSVT

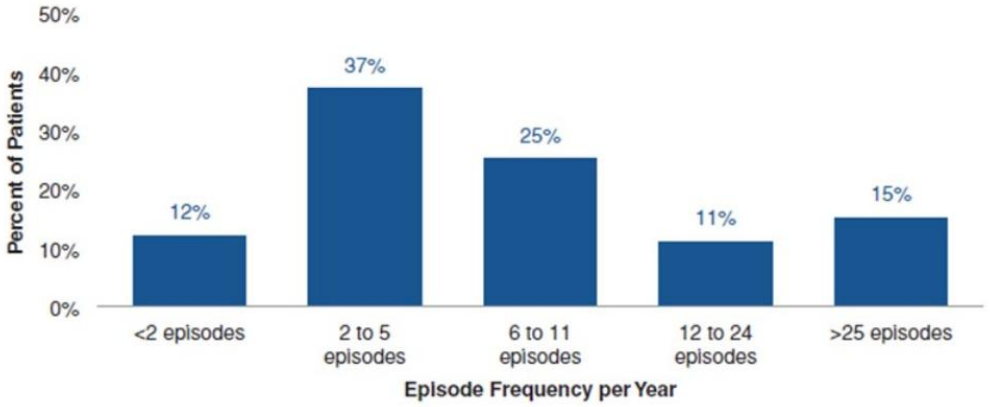
PSVT is a serious and recurring electrical disorder of the heart, which is caused by altered electrical conductivity over the AV node. PSVT refers to a rapid heart rate condition of the heart's upper chambers (atria) of abrupt onset and termination. In the most common form of PSVT called AV nodal reentrant tachycardia, or AVNRT, there is an extra piece of electrical tissue that allows the electrical signal to travel very rapidly in a circle. As shown in the figure below, when that extra tissue forms within or near the AV node, the signal can now travel down one part of the AV node and up the other in a small circle, sending impulses out to both the atria and ventricles along the way. The cycle continues over and over, resulting in a rapid heart rate.



In the next most common form of PSVT, called atrioventricular reciprocating tachycardia, or AVRT, there is an extra piece of electrical tissue that directly connects the atria and the ventricles. In AVRT, the electrical signal begins like it would in a normal heart beat by traveling from the atria to the ventricles over the AV node. However, as shown in the figure above, in AVRT, the extra piece of electrical tissue allows the signal to travel back up to the atria, creating a "short circuit." Once the signal gets back to the atria, it goes back down to the AV node and the cycle continues over and over, resulting in a rapid heart rate.

Uncertainty of the timing and duration of episodes of SVT can significantly impact patient quality of life. In 2018, we conducted a quantitative internet survey involving 256 patients with PSVT. The survey was designed to assess the impact of PSVT on patients prior to and after their diagnosis and explored the key patient drivers of disease burden, including episode frequency, duration, perceived severity of symptoms and emergency department visits. The survey included both newly diagnosed PSVT patients and patients who had been diagnosed with PSVT for some time. The previously diagnosed patients had an average time since diagnosis of seven years. This survey indicated that it takes more than two years after first experiencing symptoms of PSVT for the average patient to receive a formal diagnosis. We believe this delay in diagnosis is primarily the result of the episodic nature of the disease and the requirement for an ECG when the patient is experiencing an SVT episode to confirm the diagnosis. We estimate that, overall, 60% of PSVT patients are women and approximately half suffer from cardiovascular comorbidities. The figure below shows the surveyed patients' total number of SVT episodes in the first 12 months after diagnosis.

Total Number of SVT Episodes in the First 12 Months After Diagnosis



Patients reported episode frequencies that vary from less than one per year to greater than 25 per year. Based on this market research, we estimate that patients with PSVT experience a median of four to seven episodes of SVT per year. These episodes can be debilitating for patients, who can be left unable to focus on family or work during an episode. When in an episode of SVT, patients may experience symptoms including palpitations, sweating, chest pressure or pain, shortness of breath, sudden onset of fatigue, fainting and anxiety. Symptoms commonly reported by patients with PSVT mimic other conditions and are often mistaken for anxiety or panic attacks, especially in women. Researchers have noted that up to 27% of PSVT patients stopped driving for fear of temporary loss of consciousness, fainting or passing out. Patients have reported that the duration of SVT episodes varies widely from minutes to hours, or more. Our market research indicates that in the year of diagnosis almost 40% of patients experience two or more episodes of SVT per year that last more than 10 minutes each, and a similar percentage visit the emergency department for treatment of their PSVT at least once per year. We also estimate that 65% of PSVT patients have used chronic medications prophylactically to reduce episode frequency. Our market research also shows that after the first year of diagnosis the percentage of patients with SVT episodes lasting longer than 10 minutes and the percentage visiting the emergency department for treatment decreases modestly to approximately one-third of those surveyed. Based upon our survey responses, we believe these decreases in both duration of episodes and emergency department visits are attributable to a combination of prophylactic medication use, lifestyle changes, and proper implementation of vagal maneuvers.

Current Treatment Options for PSVT

Treatment for PSVT depends on the frequency, duration, and severity of the episodes as well as patient preference. Current options for PSVT patients to terminate an episode of SVT include vagal maneuvers, IV medication or external shock delivered in the emergency department. Additionally, some practitioners prescribe oral medications, such as calcium channel blockers, beta blockers and anti-arrhythmic drugs to be taken at the onset of an episode. However, these interventions are generally not acutely effective. Long-term strategies include chronic drug therapy to reduce the frequency of episodes and cardiac ablation to potentially cure the disease. Patients may also elect to not treat their symptoms and simply endure episodes of SVT when they occur.

Vagal maneuvers are commonly attempted to terminate an episode, with low to modest success rates. These are physiological maneuvers that stimulate the vagus nerve, which can terminate an SVT episode. These include gagging, massaging the carotid artery, holding one’s breath and bearing down (Valsalva maneuver), immersing one’s face in ice-cold water, or coughing.

Currently approved acute pharmacological therapy for the treatment of an acute episode of SVT includes IV administration of approved AV nodal-blocking agents in an acute care setting. The current standard of care for treatment of episodes of SVT is adenosine, but prior to its approval in 1990, episodes of SVT were treated with IV calcium channel blockers, such as verapamil or diltiazem. When given as a rapid IV bolus, adenosine blocks conduction over the AV node, thereby interrupting the arrhythmia circuit and restoring the heart back to sinus rhythm. Adenosine temporarily stops the heart and patients have reported experiencing chest tightness, flushing and a sense of impending death. Physicians report that patients tell them that they feel like they are going to die. Adenosine is eliminated from the body in less than one minute, but cannot be self-administered as it requires IV access. In-hospital IV administrations are associated with higher healthcare costs, and are also unsettling and inconvenient for the patient. IV calcium channel blockers also slow conduction over the AV node during the course of several minutes. However, they are associated with the risk of excessive slowing of the heart rate and low blood pressure. According to treatment guidelines, patients in the acute care setting who fail pharmacologic treatment for PSVT could then receive direct current cardioversion, where an electric shock is applied to the heart to return it to sinus rhythm.

In an attempt to prophylactically control the frequency and duration of future SVT episodes, many patients will take chronic daily oral medications that modulate AV nodal conduction, such as beta blockers, L-type non-dihydropyridine calcium channel blockers, or antiarrhythmic drugs. Despite chronic daily oral medication, breakthrough SVT episodes that require visits to the emergency department may still occur, albeit for some patients at a reduced frequency. Chronic medication can lead to side effects such as sexual dysfunction or fatigue in the case of beta blockers and constipation in the case of verapamil. Some patients discontinue chronic oral medication due to intolerable side effects. Based on our market research, we estimate that approximately two thirds of PSVT patients have been prescribed chronic medications such as beta blockers or calcium channel blockers to prevent SVT episodes.

The only potentially curative treatment available at the present time for PSVT is ablation, an invasive procedure, which works by directly cauterizing or freezing the short circuit that is the cause of the abnormal rhythm. This is achieved in an electrophysiology lab via catheters that are run through the patient's groin vessels and into the heart and uses burning or freezing techniques to destroy the heart's abnormal electrical tissue. Ablation single-procedure success rates for PSVT are reported to be 91% to 96%. However, we estimate that less than 10% of patients with PSVT per year choose this option, which we believe is due primarily to anxiety related to the procedure. Although ablations are generally considered to be safe by the treating community, as with any invasive procedure there are potential complications, which include bleeding, blood clots, pericardial tamponade, and transient or permanent heart block, with the latter requiring permanent pacemaker implantation.

Market Opportunity

We believe that PSVT is a large and under-recognized market that we estimate affects approximately two million Americans and results in over 600,000 healthcare claims in the United States alone per year, including more than 150,000 emergency department visits and hospital admissions and up to 80,000 ablations. Furthermore, we estimate that approximately 300,000 people are diagnosed with PSVT each year in the United States. We derive these estimates from the analysis of longitudinal claims data, which we believe is the most accurate method available to estimate the epidemiology of PSVT. In particular, we analyzed longitudinal Medicare claims data for patients age 65 and older and employer-based medical claims data for patients under age 65 with five or more years of continuous enrollment, for the years 2008 through 2016. We identified patients who, during this time period, had either two or more PSVT codes (ICD9 427.0 or ICD10 I47.1) in the outpatient setting or one or more of these codes in the emergency department or inpatient setting. Another prevalence analysis was published and presented at the 2018 International Academy of Cardiology's Scientific Sessions. Using four years of longitudinal claims data in patients under age 65, this analysis arrived at similar conclusions regarding the number of PSVT patients in the United States. Both of these analyses were funded by us and included participation by our employees.

Other published sources that attempt to quantify the epidemiology of PSVT, such as the MESA study published in the Journal of the American College of Cardiology in 1998, and the PREEMPT study published in the Journal of the American Heart Association in 2018, provide important demographic and clinical characteristic data on patients with PSVT. For example, in the MESA study, fewer than 40% of the adjudicated incident cases of PSVT would have been detected had the investigators limited their screening to those patients identified by the PSVT ICD-9 Code (427.0). In

addition, 21% of the incident PSVT patients in the MESA study also had a diagnosis of atrial fibrillation (18%) or atrial flutter (6%). As an epidemiology tool, however, we believe these studies underestimate the incidence and prevalence of PSVT due to the episodic nature of the disease as well as the variability in the duration of the episodes, as the investigators in both studies relied only on data from patients presenting to healthcare settings acutely, with the episode confirmed on ECG during the encounter, to estimate the incidence and prevalence of PSVT.

From market research conducted in 2017 and 2018, we estimate a core target addressable market of approximately 40-65% of the prevalent population that we estimate has a higher burden of PSVT as measured by episode frequency and duration, emergency department visits and prophylactic use of chronic medications to reduce episode frequency. We define this core addressable market as patients who have been diagnosed with PSVT and who are engaging the healthcare system for treatment of PSVT, as identified by insurance claims, on an annual basis. Beyond this core addressable market, we believe that there is a significant opportunity for etripamil to help the estimated 1.4 million patients who have been diagnosed with PSVT but do not engage in the healthcare system on an annual basis. We believe many of these patients do not seek treatment for PSVT because they are not satisfied with the current options to manage an acute episode or because they have been told by their physician that their condition is not life threatening and episodes of SVT will eventually self-terminate. We believe that these untreated patients may reengage the healthcare system if alternative treatment options are available to them. In addition, we believe that advances in digital health and wearable technology may lead to more rapid diagnosis of PSVT in the future, resulting in more patients seeking treatment for their symptoms.

Current treatment for PSVT consumes significant healthcare resources. Retrospective research on claims data partly sponsored by us and published in the American Journal of Cardiology in 2020 shows that healthcare expenditures for patients rose significantly in the year prior to PSVT diagnosis, suggesting that increasing symptoms lead patients to seek more medical care. In the year following diagnosis, mean annual healthcare expenditures nearly doubled for those less than 65 years of age and tripled for those over 65 years of age, compared to matched controls, increasing mean health care expenditures by approximately $10,000 in the less than 65 age group to approximately $20,000 per patient in the greater than 65 age group. Significant increases in emergency department visits pre- and post-diagnosis were observed for both age groups. For those less than 65, the average cost of hospitalizations doubled post-diagnosis as their mean number of hospitalizations quadrupled. Of note, catheter ablations following diagnosis represented only 23% of this increased spend in this patient group.

Looking to the broader landscape of economic burden on our health system from cardiac treatments, a 2021 retrospective study of claims data partly sponsored by us and published in the American Heart Journal found patients less than 65 years of age with PSVT in the first year after diagnosis cost the health care system a comparably similar amount on a per patient basis to patients with atrial fibrillation. This study followed patients for up to six years post-diagnosis. Similar to the previously referenced American Journal of Cardiology study, this data showed that costs never returned to baseline, which we believe indicates a need for more treatment options in long-term PSVT management.

With regard to total healthcare costs, we estimate from the assessment of claims data that approximately $3 billion is spent each year in the United States on treatments for PSVT, with 58% or $1.9 billion of annual costs being driven by ablation procedures, and 36% or $1.2 billion resulting from emergency department visits, hospitalizations and outpatient hospital visits for PSVT.

Our Clinical Development Program for the Treatment of PSVT

Current treatments do not address the unmet medical need for a rapid-acting, effective, and safe patient-administered treatment that can be taken outside of a hospital or acute care setting at the onset of an SVT episode to restore the heart back to sinus rhythm. We believe that etripamil fills this need. We completed a Phase 1 clinical trial, which supported the selection of four doses of etripamil for Phase 2 development, followed by a Phase 2 clinical trial in adult patients to evaluate the effects of those four doses in patients with PSVT. Both trials were conducted to assess nasally- administered etripamil compared to placebo. Based on discussions with the FDA, we initiated a pivotal Phase 3 clinical trial (NODE-301) in July 2018 to assess the efficacy and safety of etripamil in the at-home setting, and released topline data in March of 2020. We have completed a second Phase 1 clinical trial, further characterizing the PK and PD of etripamil in

Japanese and non-Japanese healthy volunteers. We have also completed the conduct portion of an open label Phase 3 safety trial (NODE-302), which provided further drug access to patients that had previously participated in the NODE-301 trial. The primary objective of the NODE-302 trial is to assess the safety of etripamil 70 mg in patients over multiple episodes. We are in the process of analyzing the data from that trial. We are also conducting NODE-303, which is an ongoing open label Phase 3 study that has the objective of collecting further safety data. The FDA has agreed that our Phase 3 clinical program could support an NDA filing in the United States.

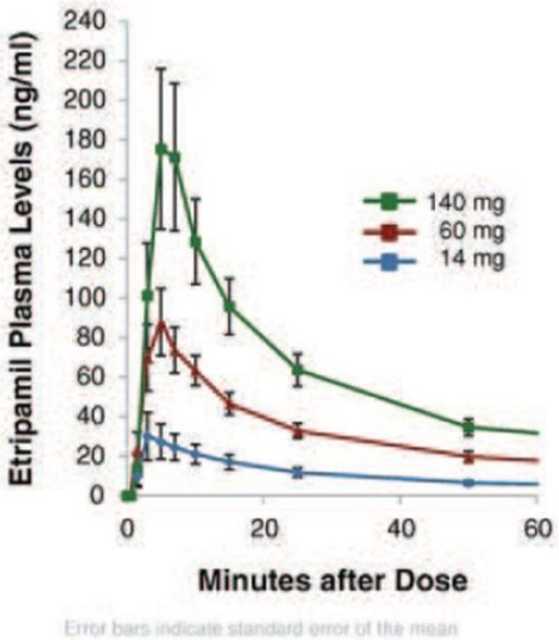
Phase 1 Clinical Data

We completed a Phase 1 clinical trial (MSP-2017-1096) in healthy volunteers, which was designed to assess the safety, PK profile, and cardiac pharmacology of intranasally administered etripamil in a randomized, double-blind, placebo controlled, single ascending dose trial. The primary objective of this trial was to determine the maximum tolerated dose or maximum feasible dose of two different formulations of etripamil administered via the nasal route in healthy, adult male subjects. All doses of etripamil were generally well tolerated, and there was no difference in the safety profile and PK between the two formulations of etripamil, referred to as MSP2017A and MSP2017B. The study of MSP2017A was stopped at 60 mg and MSP2017B was further studied at higher doses (105 mg and 140 mg). The Phase 1 results supported the selection of four doses of etripamil for Phase 2 development. We are using this Phase 1 data to support further clinical development of etripamil in two indications: PSVT and AFib-RVR.

Following nasal administration of etripamil, PK analyses demonstrated rapid absorption and elimination, a dose proportional systemic exposure, or area under the curve, and maximum plasma concentration for etripamil and its primary inactive metabolite. These findings were consistent across a range of seven doses tested up to 140 mg The 140 mg dose was the maximal feasible dose because neither the concentration (350 mg/mL) nor the volume (200 µL) of solution administered in each nostril could be increased. Due to these characteristics of formulation and delivery, a maximum tolerated dose of etripamil was not established. The figure below shows the rapid absorption via the nasal route and the rapid decrease in plasma concentration of etripamil.

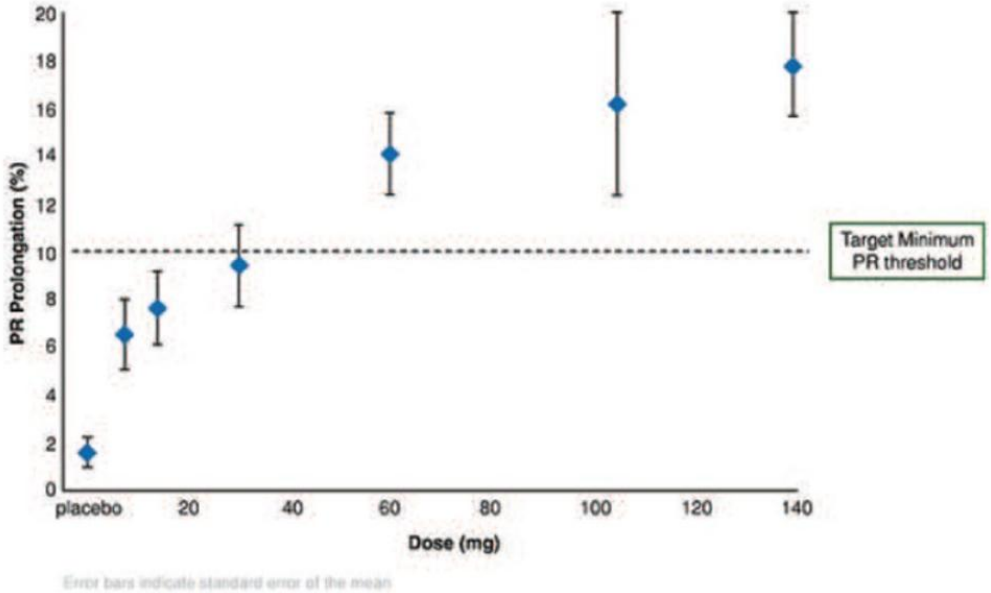
Phase 1: (MSP-2017-1096)

Pharmacokinetic Profile of Etripamil Plasma Concentrations



Prolongation of the PR interval as measured by ECGs was taken as the PD measure. A linear relationship was observed between the dose of etripamil and prolongation of the PR interval. The 60 mg, 105 mg, and 140 mg doses demonstrated a 10% or greater PR prolongation, which is shown in the figure below. This correlates with the reported slowing of conduction over the AV node that is necessary to convert an SVT episode to sinus rhythm. Such slowing of conduction has already been observed clinically with IV AV nodal-blocking agents such as adenosine, verapamil, and tecadenoson.

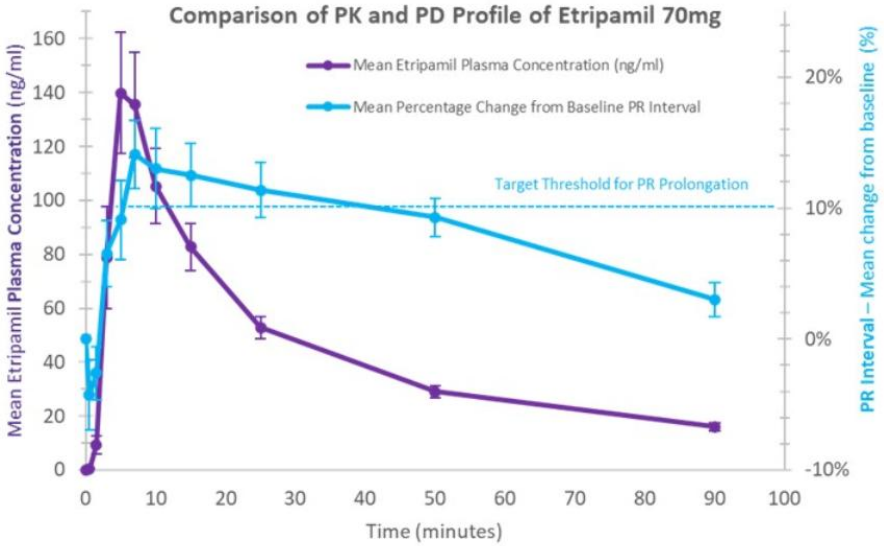
Phase 1: (MSP-2017-1096) - Pharmacology



We completed a second Phase 1 trial, NODE-102, comparing the PK and PD of etripamil 35 mg, 70 mg, and 105 mg versus placebo in Japanese and non-Japanese healthy volunteers. Once we determined there was no difference in PK and PD of etripamil between Japanese and non-Japanese participants, we pooled the data from the overall populations into a single dataset. We believe this trial provides further justification for the selected 70 mg dose in our Phase 3 program, and may be used to support further clinical development of etripamil in Japan.

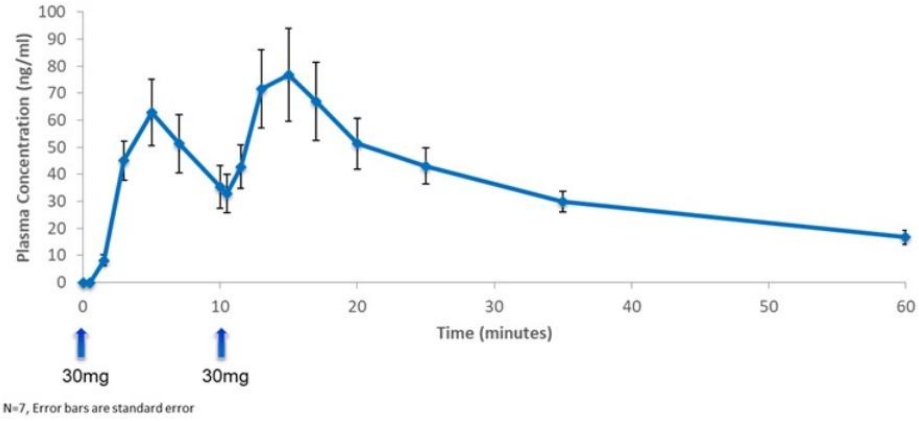
As shown in the figure below, we observed a correlation between the PK profile of etripamil 70 mg, measured by change in PR interval from baseline over time, and the plasma concentrations of etrimpamil. With regard to pharmacodynamics, we believe an approximately 10% increase in the PR interval is a marker of meaningful AV nodal conduction needed to terminate an episode of PSVT. The data as demonstrated on the blue line on the graph below indicates that etripamil 70 mg is potentially impacting AV nodal conduction at meaningful levels for a period up to approximately 50 minutes.

Phase 1: (MSP-2017-1205) NODE-102



As noted in the discussion of the RAPID study below, the RAPID study will incorporate a repeat dose administration regimen of study drug (either 70 mg of etripamil or placebo). Specifically, patients will be instructed to administer a repeat administration of study drug if they have not experienced symptom relief within 10 minutes of the first study drug administration. This tailored regimen utilizes a repeat-dose similar to current PSVT treatment practices with intravenous drugs in the emergency department setting. A similar regimen, using repeat doses of 30 mg etripamil administered 10 minutes apart, was tested in one cohort of the original phase 1 trial (study MSP-2017-1096). As shown in the figure below, this regimen allowed for greater systemic exposure to etripamil in this cohort, as measured by a second maximum concentration after the second administration, as well as a total Area Under the Curve. We believe this data supports the hypothesis underlying our RAPID trial regimen that a second administration will increase bioavailability and result in a greater therapeutic effect.

Phase 1: (MSP-2017-1096) -30 mg etripamil administered 10 minutes apart

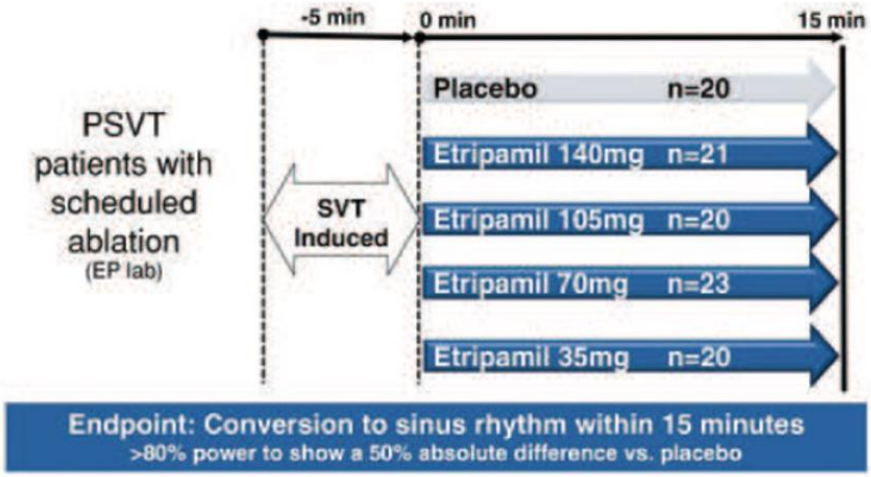


Phase 2 Clinical Data

We completed a Phase 2 multicenter, randomized, double-blind, placebo controlled clinical trial in the United States and Canada to evaluate the effects of four different doses of etripamil in patients with PSVT. In order to demonstrate the ability of etripamil to terminate SVT in a controlled setting, we conducted the study in the electrophysiology, or EP, laboratory setting, where the SVT episode could be induced in patients scheduled to undergo an EP study and ablation. The primary objective of this trial was to demonstrate the superiority of at least one dose of etripamil over placebo in terminating SVT. The secondary objectives were to determine the minimally effective dose of etripamil, to establish a dose related efficacy trend for etripamil, and to evaluate the safety of etripamil in a clinical setting. The trial was statistically powered at more than 80% to show a 50% absolute difference of etripamil versus placebo.

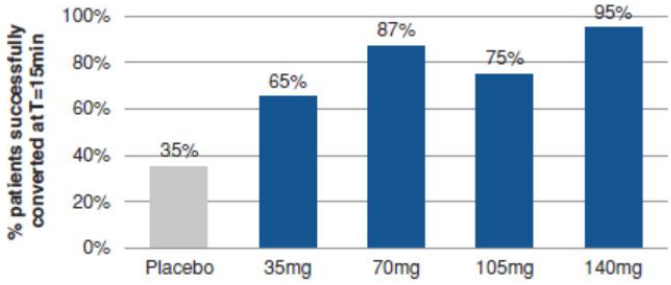
The trial enrolled 199 patients, of which 95 withdrew prior to dosing: 70 due to inability to induce (n=42) or sustain (n=28) SVT, 5 based on physician discretion, 1 lost to follow up, 1 due to withdrawal of consent, and 18 for other reasons. The mean age of patients was 52.2 years, with the study enrolling patients as young as 19 and as old as 85. As shown in the figure below, SVT was induced and sustained for 5 minutes in 104 patients, who were randomized into one of five dosing cohorts. Four cohorts received active doses of etripamil (35 mg, 70 mg, 105 mg or 140 mg) and one cohort received placebo. All doses of the study drug were delivered in a blind randomized fashion in which healthcare providers administered four 100 µL sprays from four different single spray devices. There were no imbalances in baseline characteristics across the five treatment groups. The mean heart rate in SVT at time 0 was 177 bpm in the placebo group and 168 bpm, 173 bpm, 180 bpm and 155 bpm in the etripamil 35 mg, 70 mg, 105 mg and 140 mg groups, respectively.

Phase 2: (MSP-2017-1109) NODE 1 – Clinical Trial Design



The primary endpoint in this clinical trial was the conversion of SVT to sinus rhythm within 15 minutes after administration of etripamil or placebo. As shown in the figure below, the percentage of patients in whom SVT converted to sinus rhythm within 15 minutes of study drug administration was 65% with 35 mg etripamil, 87% with 70 mg, 75% with 105 mg and 95% with 140 mg, compared with 35% in the placebo arm. The three highest doses of etripamil showed statistically significant conversion rates compared with placebo. Statistical significance expresses the probability that the results of a particular study could have occurred purely by chance. Statistical significance is assessed by the FDA and other health regulatory agencies in evaluating marketing approval applications. FDA and other regulatory agencies review the strength of the statistical evidence and whether it supports the claims of the applicant. The primary endpoint, statistical methods for the trial and a p-value boundary for achieving statistical significance for a clinical trial are typically defined before the trial begins. If the probability of observing the calculated statistic is smaller than the p-value boundary, the primary endpoint is considered statistically significant. P-value is a conventional statistical method for measuring the statistical significance of clinical results. A p-value of 0.05 or less represents statistical significance, meaning there is a less than 1in 20 likelihood that the observed results occurred by chance. The FDA utilizes statistical significance, as measured by p-value, as an evidentiary standard of efficacy and typically requires a p-value of 0.05 or less to demonstrate statistical significance.

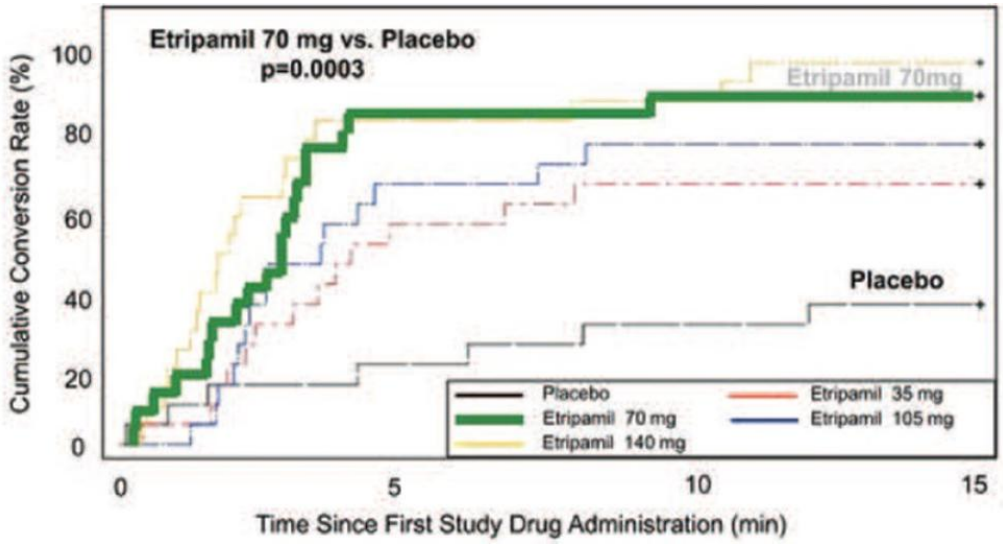
Phase 2: (MSP-2017-1109) NODE 1 - Etripamil Conversion Rates from SVT to Sinus Rhythm



# patients converted at 15 min	7/20	13/20	20/23	15/20	20/21
p-value		0.1128	0.0006	0.0248	<.0001

In a post-hoc analysis conducted to help inform our Phase 3 trial design, the patients' time to conversion to sinus rhythm was examined. As shown in the following Kaplan Meier plot of patients successfully converting to sinus rhythm during the 15 minute study window, the three highest doses of etripamil (140 mg, 105 mg and 70 mg) showed statistically significant shorter time to conversion compared with placebo. The 70 mg dose showed a rapid onset of action with a median time to conversion of less than three minutes after nasal administration of etripamil.

Phase 2: (MSP-2017-1109) NODE 1 – Etripamil Time to Conversion from SVT to Sinus Rhythm



Overall, etripamil was well tolerated, and the most common adverse events were related to the nasal route of administration, e.g., nasal irritation or nasal congestion, reported by up to 60% and 45% of patients, respectively, after

etripamil versus none after placebo administration. The 70 mg dose was reported to have 48% nasal irritation and 26% nasal congestion. However, these were transient. Most adverse events were mild (44.2%) or moderate (24.0%) across all treatment groups. At least one adverse event considered related to the study drug, according to the investigator assessment, was reported in 17 (85.0%) patients in the etripamil 35 mg group, 18 (78.3%) in the 70 mg group, 15 (75.0%) in the 105 mg group, 20 (95.2%) in the 140 mg group and 4 (20.0%) in the placebo group. The incidence of adverse events was not dose dependent. Hypotension, or low blood pressure, was reported as an adverse event in two patients, one in the 105 mg dose group of etripamil and one in the 140 mg group.

A total of three patients experienced severe adverse events that were considered possibly related to etripamil. One patient who received a 35mg dose of etripamil experienced facial flushing, shortness of breath, and chest discomfort. One patient who received a 105 mg dose of etripamil had nausea and vomiting, as well as a severe and serious cough. One patient who received a 140 mg dose of etripamil experienced a severe adverse event of second-degree AV block with hypotension beginning five minutes after conversion to sinus rhythm. The AV block resolved after 43 minutes and ablation was subsequently performed. There were no adverse events that led to study discontinuation or death.

Calcium channel blockers have the potential to cause hypotension as a side effect. In our Phase 2 clinical trial, we recorded vital signs, including heart rate and blood pressure, before induction of SVT and every two minutes for 30 minutes after study drug was given. We observed no meaningful reduction in mean blood pressure in the 35 mg or 70 mg etripamil cohorts, but observed a transient decrease in the mean blood pressure in the two highest cohorts, 105 mg and 140 mg. Due to the induction of SVT, the mean systolic blood pressure decreased at time 0 compared to the average at 20 and 10 minutes before SVT induction. Compared to baseline and time 0, systolic blood pressure measurements recorded from 2 minutes to 16 minutes post study drug administration showed no decrease in mean systolic blood pressure in the placebo or 35 mg groups, and maximum mean decreases of 2 mmHg four minutes post dose in the 70 mg group, 17 mmHg six minutes post dose in the 105 mg group, and 20 mmHg six minutes and eight minutes post dose in the 140 mg group.

Based on the combination of efficacy and safety data from our Phase 2 trial, we selected the 70 mg dose of etripamil for our subsequent clinical trials. There was no decrease in mean systolic blood pressure compared to baseline from 16 to 30 minutes post-study drug administration.

Ongoing and Planned Clinical Development of PSVT

In July 2020 we announced that we received guidance from the FDA on our proposal to use data from the outcome of the NODE-301 trial as well as the ongoing RAPID trial. . After discussions with the FDA, we determined that the RAPID trial will be randomized to a placebo controlled double blinded dosing regimen that will permit a second 70 mg dose of etripamil to be administered if symptoms persist for 10 minutes after the first dose. Under an updated statistical analysis plan, the primary efficacy endpoint for both the RAPID trial and the NODE-301 trial will be defined as the difference between active drug and placebo in time to termination of an episode of PSVT and conversion to sinus rhythm within 30 minutes of study drug administration for events confirmed to have been PSVT, with a target p-value of less than 0.05 for each trial. The FDA agreed that the single and repeat administrations of etripamil could be pooled and compared to placebo for the primary analysis, resulting in no increase in the trial's sample size. The FDA further indicated that the two trials, NODE-301 and RAPID, could potentially fulfill the efficacy requirement for our planned NDA for etripamil in patients with PSVT.

We also had an end of Phase 2 meeting with the FDA in September 2017 to review our Phase 2 clinical trial results and to discuss our proposed Phase 3 clinical program. The FDA agreed with our proposal to assess the efficacy of etripamil in PSVT patients in the at home setting and suggested that we consider conducting a single pivotal trial to assess the efficacy of etripamil, followed by two open label safety trials. The FDA further confirmed that a large outcome trial would not be required for etripamil and that the total NDA safety database could consist of up to 1,500 patients. We also had a meeting to obtain Scientific Advice from the European Medicines Agency, or EMA, in April 2018. The EMA agreed that our planned Phase 3 program could support a registration in the European Union but recommended additional safety data in noninduced episodes of SVT.

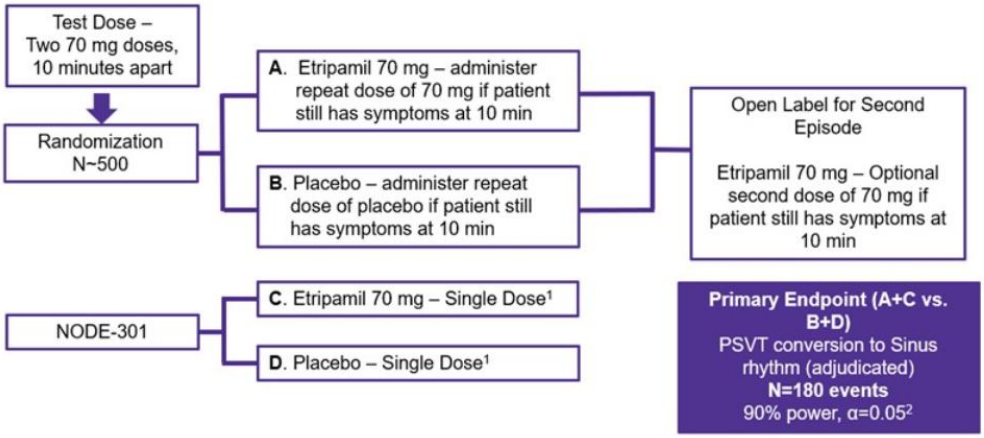
In summary, based on our interactions with the regulatory agencies, our planned Phase 3 clinical program includes:

- NODE-301, a pivotal efficacy trial to assess the time to conversion of etripamil compared to placebo in the at-home setting;
- RAPID Study, a confirmatory pivotal efficacy trial to assess the time to conversion of etripamil compared to placebo in the at-home setting;
- NODE-302, an open-label extension of NODE301 to enroll patients who have completed NODE301 in order to collect safety data on subsequent episodes; and
- NODE-303, an open-label global safety trial to complete the safety assessment of etripamil in the at-home setting to support an NDA.

Phase 3 Clinical Trials

RAPID. The RAPID trial was originally an ongoing trial named NODE-301B and was designed to collect double-blind data from randomized patients who had not yet experienced an SVT event after the NODE-301 study reached its target number of adjudicated SVT events. After receiving guidance from the FDA on our Phase 3 program, we have amended and expanded NODE-301B and renamed it the RAPID trial. The RAPID trial will include the 170 patients who are already enrolled in NODE-301B and is expected to enroll approximately 500 patients. The trial will be completed after a total of 180 confirmed SVT events are reached. Additional patients to be enrolled in the RAPID trial will be randomized 1:1. The graphic below shows the design of the RAPID trial.

Phase 3: (MSP-2017-1138) RAPID – Trial Design

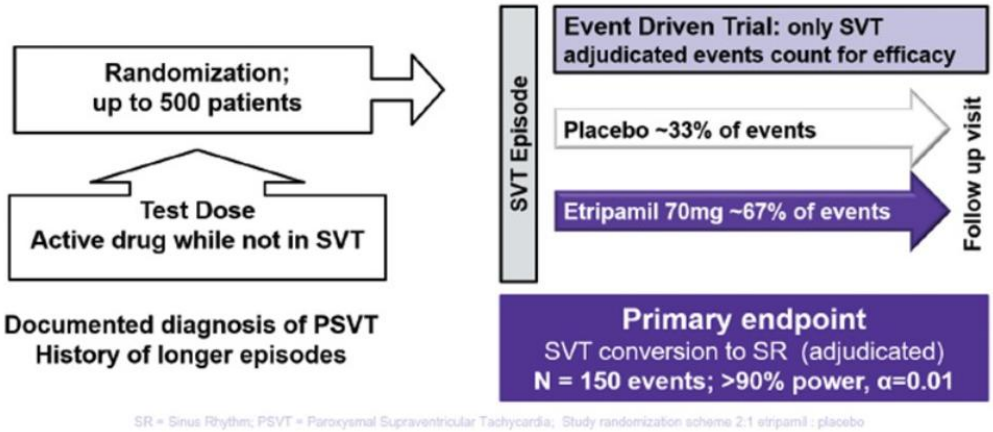


(1) Arms C and D (single dose) will be only the patients enrolled under NODE-301 who have had an episode prior to the RAPID Study protocol amendment
(2) Wilcoxon analysis modeling from NODE-301 data

The RAPID study is planned to be conducted in North America and in multiple countries in Europe. The trial was initiated in North America during the fourth quarter of 2020, amidst the COVID-19 pandemic. The first patient was dosed in November 2020.

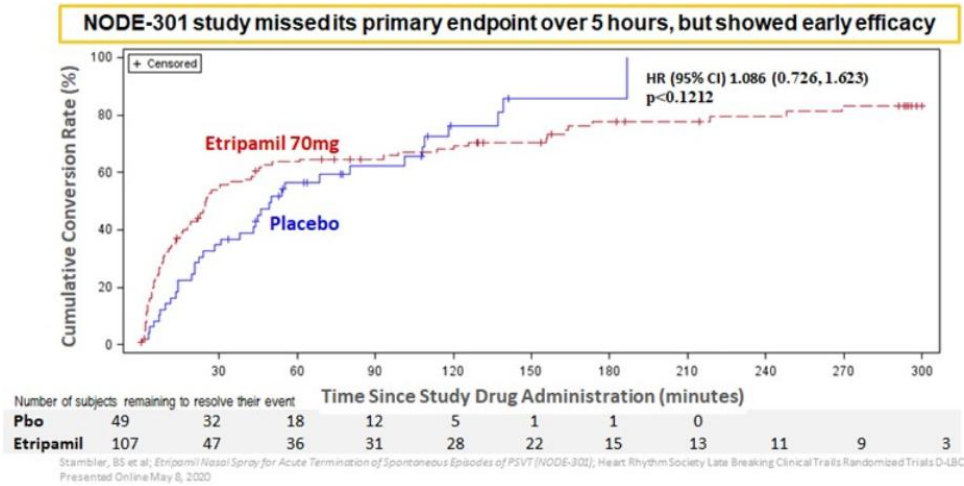
NODE-301. NODE-301 is a placebo controlled Phase 3 clinical trial conducted in the United States and Canada to evaluate 70 mg of etripamil versus placebo in terminating an SVT episode in the at-home setting. As shown in the figure below, the primary endpoint is the time to conversion over a five hour monitoring period following the administration of the study drug. Prior to randomization, eligible patients administered a test dose of 70 mg of etripamil in the investigator's office while in sinus rhythm in order to assess tolerability. Patients successfully completing the test dose were randomly assigned to the etripamil or placebo cohorts (2:1 randomization) and sent home with the study drug and a small portable cardiac monitor to be used during the patient's subsequent SVT episode. Upon experiencing symptoms of their next SVT episode, patients were instructed to first apply the cardiac monitoring device to record ECG data, then attempt a vagal maneuver, and if that was not successful in terminating the episode, to then administer the drug. Patients' ECG data was recorded using the cardiac monitoring device for a period of five hours after study drug administration. Patients returned to the clinic for a follow up visit within one week following their SVT event for collection of further information. NODE-301 enrolled 431 patients across 65 sites in the United States and Canada, with 156 patients (107 etripamil, 49 placebo) receiving etripamil for an adjudicated true PSVT episode.

Phase 3: (MSP-2017-1138) NODE-301 Part 1 - Clinical Trial Design



In March 2020, we reported topline results of the first part of the NODE-301 trial. The first part of NODE-301 did not meet its primary endpoint of time to conversion of SVT to sinus rhythm compared to placebo over the five hour period following study drug administration. The median time to conversion for etripamil was 25 minutes (95% CI: 16, 43) compared to 50 minutes (95% CI: 31,101) for placebo. As shown in the top figure below, despite etripamil's activity and separation from placebo in the first approximately sixty minutes following study drug administration, a time period consistent with etripamil's pharmacological activity, results from the latter part of the analysis confounded the statistical analysis of the primary endpoint. We also analyzed the first 30 minutes of the kaplain meir curve, shown in the bottom graph below, and the post hoc results at that time point were a 54% rate of conversion for the etripamil patients and 35% for the placebo patients. The results were statistically significant with a hazard ratio of 1.87 and a p-value of 0.02.

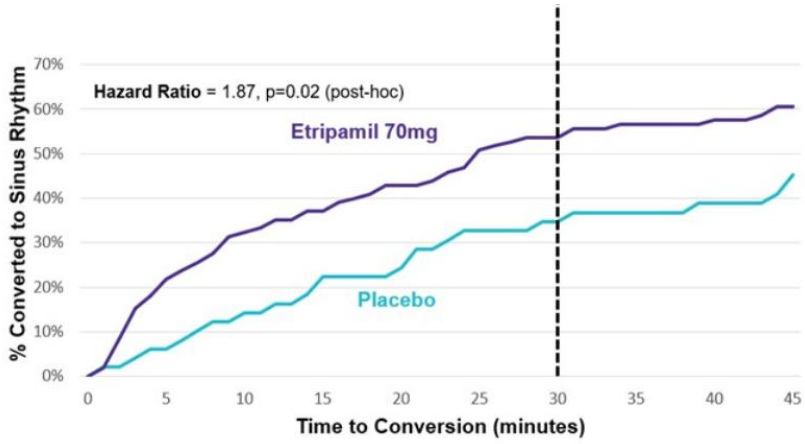
Phase 3: (MSP-2017-1138) NODE-301 Part 1 Efficacy – Time to Conversion over 5 Hours



Stambler, BS et al; *Etripamil Nasal Spray for Acute Termination of Spontaneous Episodes of PSVT (NODE-301)*; Heart Rhythm Society Late Breaking Clinical Trails Randomized Trials D-LBCT01; Presented Online May 8, 2020

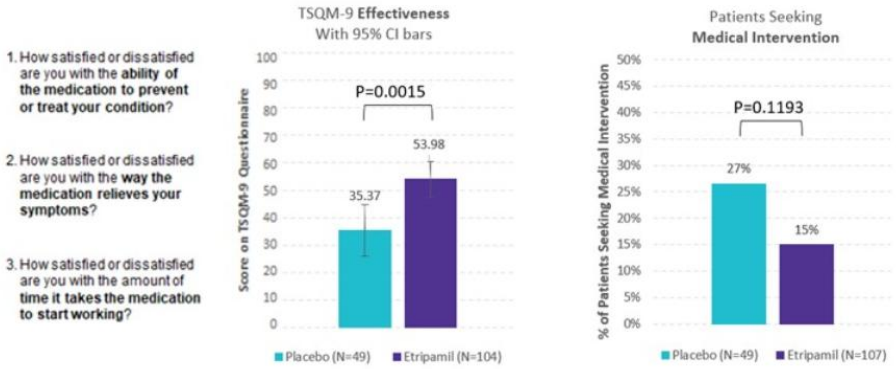
Phase 3: (MSP-2017-1138) NODE-301 Part 1 Efficacy – Time to Conversion up to 30 Minutes

Post-hoc analysis: 70 mg etripamil dose showed rapid time to conversion (median ~25 min)



The study demonstrated statistically significant improvements in patients taking etripamil compared to those taking placebo in the secondary endpoint of patient reported treatment satisfaction, as measured by a treatment satisfaction questionnaire for medication (TSQM-9), including global satisfaction (p=0.0069) and effectiveness scores (p=0.0015). Additionally, there was a trend towards improvement in the percentage of patients seeking rescue medical intervention, including in the emergency department, with 15% and 27% etripamil and placebo patients, respectively, reporting such intervention (p=0.12).

Phase 3: (MSP-2017-1138) NODE-301 Part 1
Key secondary endpoints from NODE-301 support benefit of etripamil to patients and payors



NODE302. NODE302 is the open label extension trial of NODE301. We designed NODE302 to evaluate the safety of etripamil when self-administered without medical supervision and to monitor the safety and efficacy of etripamil for the treatment of multiple episodes of SVT.

Patients who have successfully dosed with the study drug in NODE-301 and completed a study closure visit were eligible to enroll in NODE-302 to manage any subsequent episodes of SVT. Eligibility was also contingent on satisfying all inclusion and exclusion criteria, including not experiencing a serious adverse event related to the study drug or the study procedure that precludes the self-administration of etripamil.

We initiated NODE302 in December 2018. The trial completed enrollment in 2020 and data is expected to be available in 2021.The safety results will contribute to the etripamil safety database.

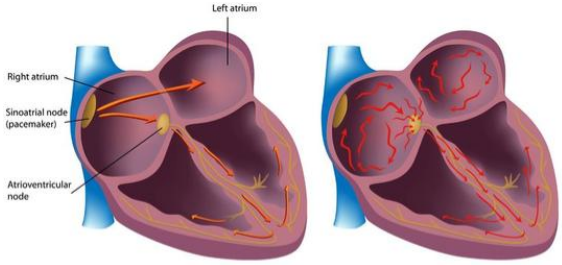
NODE303. NODE-303 is an open-label global safety trial enrolling up to 3,000 patients who did not participate in NODE-301 or NODE-302 in order to collect data on up to 1,000 patients taking etripamil in an at-home setting. We designed NODE-303 to evaluate the safety of etripamil when self-administered without medical supervision, and to evaluate the safety and efficacy of etripamil on multiple SVT episodes. The patients have the opportunity to manage up to four episodes of SVT in NODE-303.

NODE-303 was initiated in October 2019. Based on a review of the NODE-301 safety data available in June 2019, the FDA and multiple European and Latin American regulatory authorities agreed to allow patient enrollment in NODE-303 without an in-office safety test dose and in a broad patient population, including patients taking concomitant betablockers and calcium channel blockers.

Atrial Fibrillation

Atrial fibrillation is a common form of arrhythmia with an irregular and often rapid heart rate that can increase the risk of stroke, heart failure, and other heart-related complications. During AF, the heart's two upper chambers, the atria, beat chaotically and irregularly—out of coordination with the two lower chambers, the ventricles, of the heart, as shown in the figure below. AF can occur with or without symptoms, with symptoms often including heart palpitations, shortness of breath, and weakness. Episodes of atrial fibrillation can come and go, or patients may have AF that does not resolve. Although the heart arrhythmia in AF itself usually is not life-threatening, it is a serious medical condition that sometimes requires emergency treatment. Additionally, AF is associated with elevated risk of embolism and stroke and

anticoagulant medications, also called blood thinners, are commonly prescribed to manage this risk. Uncertainty around symptom timing and episode length may impact a patient's quality of life.



Classification of AF is used to determine the appropriate treatment modality for patients. The American Heart Association, or AHA, and the American College of Cardiology, or ACC, categorize AF patients based on disease progression. These categories are defined as follows: paroxysmal ,which involves AF episodes that resolve spontaneously within seven days of symptom onset; persistent, which involves AF episodes that fail to terminate within seven days of symptom onset and require treatment to convert back to sinus rhythm; long-standing persistent, which involves AF atrial fibrillation episodes that last longer than one year despite continued attempts to restore sinus rhythm; and permanent, which involves a joint decision by the treating provider and patient to no longer pursue cardioversion and leave the patient in AF, focusing on rate control and symptom management. Disease progression in AF is common with approximately 25% of AF patients in the paroxysmal stage, 25% of AF patients in the persistent and long-standing persistent stage, and 50% of AF patients in the permanent stage. For purposes of simplicity, we do not differentiate the long-standing persistent classification from the persistent classification as the clinical impact of this differentiation has not been characterized. Concomitant structural heart irregularities including valvular dysfunction and the presence of active symptoms may also help to characterize patients and influence treatment decisions.

A common complication of atrial fibrillation is rapid ventricular rate which is frequently defined as a heart rate of ≥110 beats per minute. Rapid, irregular, and inefficient contractility induced by rapid ventricular rate accounts for hemodynamic instability and symptoms of palpitations. Frequently, new-onset patients with atrial fibrillation present with symptoms related to rapid ventricular rate.

Current Treatment Options for AF

There are currently two pharmacological approaches to managing atrial fibrillation: rate control to lower a rapid heart rate and rhythm control to restore and maintain a regular (sinus) rhythm and prevent recurrent AF episodes. Either of these pharmacological management approaches may be administered chronically or acutely, depending on patient preference and episode frequency and/or severity. The decision to pursue rate and/or rhythm control for AF episodes is dependent on a variety of factors, including episode severity, episode frequency, patient preference, and safety and tolerability of treatments. Several rhythm control strategies exist, including electrical cardioversion, catheter ablation and anti-arrhythmic drug therapy. For rate control, the rapid heart rate of atrial fibrillation is typically treated with AV nodal blocking drugs (for example, calcium channel blockers, beta blockers, or less commonly digoxin) to control symptoms and improve cardiac function/hemodynamic stability. Oral rate control drugs used acutely do not provide immediate ventricular rate control due to a 30-to-60-minute delayed onset of action. Breakthrough episodes of symptomatic AF often require urgent medical treatment with IV calcium channel blockers and beta-blockers under medical supervision, usually in the emergency department to quickly reduce heart rate before transitioning a patient back to oral therapy.

The "pill-in-pocket" anti-arrhythmic strategy is described by the AHA and ACC guidelines as the utilization of an oral dose of flecainide or propafenone as an attempt to restore sinus rhythm shortly after the onset of symptomatic atrial fibrillation. Neither drug referenced in the guideline is approved by any regulatory agency for the use outlined in the guideline. Pill-in-pocket rhythm control strategies are considered by physicians for patients who demonstrate favorable

outcomes to these medications in the clinic and who are thought to be reliable enough to administer them appropriately. Initial administration of pill-in-pocket medication is recommended in a monitorable setting due to potential AV node dysfunction or a proarrhythmic response and may be preceded by beta-blocker or calcium channel blocker therapy if the patient is not chronically rate controlled.

Rate controlling agents (for example, calcium channel blockers and beta blockers) may also be administered acutely on an as needed (or PRN) basis. Though the AHA and ACC guidelines do not explicitly acknowledge this approach, participants in market research conducted by us indicate a significant share of patients are managed this way. PRN rate control is more prominently used in paroxysmal patients who do not tolerate chronic medications but experience symptomatic, infrequent AF episodes. Our patient market research from 2018 estimated that approximately 40% of patients use an additional rate control medication to manage acute symptoms of atrial fibrillation. Additionally, our physician market research commissioned in 2021 suggests that both clinical/interventional cardiologists and electrophysiologists prescribe PRN rate control for some of their paroxysmal and persistent patients.

Market Opportunity – AF

The American Heart Association estimates that in 2016 approximately five million people suffered from AF in the United States. This estimate is projected to increase over the next ten years; the AHA suggests a prevalence of seven million by 2030, while the Centers for Disease Control (CDC) reports this prevalence as increasing to 12 million over the same time period, representing an approximately 6% annual growth rate. We estimate that approximately 25% of these patients have paroxysmal AF, 25% have persistent AF, and 50% have permanent AF. Acute episodes of symptomatic AF are often treated with the approaches described above. However, due to the concerning nature of AF symptoms, patients often present to the emergency department. In the ED, patients are treated with IV calcium channel blockers or beta-blockers to quickly reduce heart rate and/or anti-arrhythmic or electrical cardioversion before transitioning a patient back to oral therapy. According to the Healthcare and Utilization Project, 660,000 patient visits to the emergency department in 2016 were attributed to AF (ICD-10 diagnosis codes I48.0, I48.1, I48.2, I48.91). Additionally, approximately 465,000 patients were admitted to the hospital with AF (same ICD-10 codes).

Our initial qualitative market research indicates that the target addressable market for etripamil in patients with AFib-RVR is approximately 40% of the five million patients with atrial fibrillation. We derive this percentage estimate from a 2021 market research study conducted by us that involved qualitative interviews with a total of 25 electrophysiologists, general cardiologists, and interventional cardiologists. The physicians were asked to estimate the share of patients experiencing ≥1 symptomatic episode of AFib-RVR requiring treatment per year. In response, physicians reported approximately 60% of paroxysmal patients, 50% of persistent patients, and 30% of permanent patients met this classification. This research suggests the share of patients experiencing ≥1 symptomatic episode of AFib-RVR requiring treatment may constitute 40% of the prevalent atrial fibrillation population on a weighted average basis.

We believe that etripamil has the potential to be developed such that it can be used by patients to rapidly reduce their heart rate in the at-home setting to provide a supplemental option to the acute oral rate or rhythm control strategy their physician has already prescribed. When presented with a target product profile reflecting this potential use case, approximately two thirds of the physicians in the 2021 market research study perceived utility in the product profile, , which would serve as a “bridge” to the onset of acute oral agents. According to physicians, it can takes hours for patients to feel an alleviation of symptoms using acute oral rate and rhythm control. During this time, patients may experience frightening symptoms that often prompt them to seek emergent care. We believe that the combination of convenient delivery, potency, rapid-onset and short duration of action of etripamil has the potential to move the current treatment setting for some acute episodes of AFib-RVR out of the burdensome and costly emergency department.

Current atrial fibrillation management consumes significant healthcare resources in the United States. The American Heart Association published a report in 2016 summarizing the current and projected cost burden of cardiovascular diseases in the United States. This report suggests atrial fibrillation resulted in $25 billion in direct medical costs in 2016 (~7% of all cardiovascular diseases) and another $7 billion in indirect costs (i.e., $32 billion in total costs). Additionally, the forecasted growth in atrial fibrillation prevalence is anticipated to result in healthcare expenditures of $46 billion in direct costs and $10 billion in indirect costs in the United States by 2030.

Clinical Development Plan for Atrial Fibrillation

We began enrollment in our Phase 2 proof-of-concept clinical trial in the first quarter of 2021to evaluate the potential effectiveness of etripamil to reduce ventricular rate in patients with atrial fibrillation and rapid ventricular rate for whom IV administered calcium channel blockers have been used effectively. The Phase 2 double blind, placebo controlled, proof-of-concept, which will be conducted in Canada in collaboration with the Montreal Heart Institute and other research centers, is expected to enroll approximately 50 patients randomized 1:1 to receive either 70 mg of etripamil nasal spray or placebo. The primary endpoint will assess reduction in ventricular rate, with key secondary endpoints including the time to achieve the maximum reduction in rate and the duration of the effect.The trial is to be conducted in the hospital or emergency department setting under medical supervision. We anticipate reporting data from this study following disclosure of top line results of the RAPID trial.

Etripamil in Other Therapeutic Applications

Our goal in expanding our pipeline around etripamil is to apply the same paradigm-changing aspiration that we have for supraventricular tachycardias like PSVT and AF to other cardiac and potentially non-cardiac conditions where we believe that a rapid-onset, short-acting dihydropyridine L-type calcium channel blocker could potentially deliver significant clinical and quality of life benefits for patients. We believe that the same insights that led to the development of etripamil for the treatment of PSVT are relevant in other indications where AV-nodal blocking agents with blood vessel widening activity have demonstrated clinical utility. Both calcium channel blockers and beta blockers are commonly used to manage not only supraventricular tachycardias like PSVT or AF, but also for the treatment of chronic stable angina and angina due to coronary artery spasm.

Sales and Marketing

Given our stage of development, we have not yet established a commercial sales and marketing organization or distribution capabilities. We currently have exclusive global development and commercialization rights for etripamil for all indications that we may pursue and believe that we can maximize the value of etripamil by retaining commercialization rights in the United States and entering into collaboration agreements for certain territories outside the United States. Our current strategy is to market etripamil in the United States for the treatment of PSVT using a targeted direct sales force focused on clinical cardiologists, electrophysiologists, and high-volume primary care physicians who have a history of prescribing anti-arrhythmic therapies. We believe that a majority of PSVT patients are managed by these cardiovascular specialists and that a targeted sales force will be able to reach a substantial portion of the market for etripamil.

Manufacturing

We currently rely on third party contract manufacturing organizations, or CMOs, for all of our required raw materials, nasal spray device, API and finished product for our clinical trials and for our preclinical research. We require all of our CMOs to conduct manufacturing activities in compliance with current good manufacturing practice, or cGMP, requirements. We have assembled a team of experienced employees and consultants to provide the necessary technical, quality and regulatory oversight over our CMOs and have implemented a comprehensive plan for audits of our CMOs. Currently, we have development contracts and quality agreements with our CMOs for the manufacturing of etripamil drug substance and drug product. We currently have enough manufactured supply of etripamil to complete our ongoing registration trials. We also may elect to pursue additional CMOs for manufacturing supplies of regulatory starting materials in the future and for the filling of the nasal spray device, labeling, packaging, storage and distribution of investigational drug products. We plan to continue to rely on third party manufacturers for any future trials and commercialization of etripamil, if approved. We anticipate that these CMOs will have capacity to support commercial scale production, but we do not have any formal agreements at this time with these CMOs to cover commercial production. We believe we can identify and establish additional CMOs to provide API and finished drug product without significant disruption to our business or clinical development timelines. If etripamil is approved by any regulatory agency, we intend to enter into agreements with a third party contract manufacturer and one or more backup manufacturers for the commercial production of etripamil.

Competition

Drug development is highly competitive and subject to rapid and significant technological advancements. Our ability to compete will significantly depend upon our ability to complete necessary clinical trials and regulatory approval processes, and effectively market any drug that we may successfully develop. Our current and potential future competitors include pharmaceutical and biotechnology companies, academic institutions and government agencies. The primary competitive factors that will affect the commercial success of etripamil or any other product candidate for which we may receive marketing approval include efficacy, safety, tolerability, dosing convenience, price, coverage and reimbursement. Many of our existing or potential competitors have substantially greater financial, technical and human resources than we do and significantly greater experience in the discovery and development of product candidates, as well as in obtaining regulatory approvals of those product candidates in the United States and in foreign countries.

Our current and potential future competitors may also have significantly more experience commercializing drugs that have been approved for marketing. Mergers and acquisitions in the pharmaceutical and biotechnology industries could result in even more resources being concentrated among a small number of our competitors.

Accordingly, our competitors may be more successful than us in obtaining regulatory approval for therapies and in achieving widespread market acceptance of their drugs. It is also possible that a competitor may develop a cure or more effective treatment method for the diseases we are targeting, which could render our current or future product candidates non-competitive or obsolete, or reduce the demand for our product candidates before we can recover our development and commercialization expenses.

We are not aware of any approved drug or any drug candidate in clinical development for a patient with PSVT to self-administer treatment to terminate SVT episodes. In the acute setting, IV treatments of generic drugs such as adenosine, verapamil and diltiazem, are routinely given. Additionally, some practitioners prescribe oral medications, such as calcium channel blockers, beta blockers and antiarrhythmics to be taken at the onset of an episode. However, these interventions are not acutely effective and are not approved by the FDA or other regulatory agencies for this use.

For atrial fibrillation, there are a number of marketed generic anti-arrhythmic drugs that are used for chronic and/or acute rate control, such as metoprolol, propranolol, esmolol, pindolol, atenolol, nadolol, verapamil and diltiazem. We are aware of several drugs or new formulations of existing drugs under development or recently under development for atrial fibrillation, including InRhythm (flecainide), a sodium channel blocker in Phase II from InCarda Therapeutics, Inc., and Gencaro (bucindolol hydrochloride), a beta blocker in Phase 2 from ARCA biopharma, Inc.

Intellectual Property

We have filed numerous patent applications pertaining to etripamil and possible future product candidates, formulations containing etripamil, methods of making such formulations and clinical use. We strive to protect and enhance the proprietary technology, invention and improvements that are commercially important to the development of our business by seeking, maintaining, and defending our intellectual property. We also rely on know-how, continuing technological innovation and potential in-licensing opportunities to develop, strengthen and maintain our position in the field of cardiac arrhythmias, such as PSVT, and immediate rate control in atrial fibrillation, as well as other medical conditions affecting the cardiovascular system. Additionally, we intend to rely on regulatory protection afforded through data exclusivity and market exclusivity, as well as patent term extensions, where available.

As of March 9, 2021, our patent portfolio as it pertains to etripamil included:

- a patent family containing six U.S. patents, projected to expire in 2028, a pending U.S. patent application, which, if granted, is projected to expire in 2028, as well as corresponding patents in Australia, Brazil, Canada, China, Europe, Hong Kong, India, Japan, Mexico, New Zealand and South Korea, directed to etripamil, pharmaceutical compositions including etripamil, and uses of etripamil such as to treat angina or cardiac arrhythmias, including PSVT and atrial fibrillation; and

- a patent family containing one U.S. patent, projected to expire in 2036, a pending U.S. patent application, which, if granted, is projected to expire in 2036, as well as corresponding patents in Australia, Europe, Hong Kong, Japan, Mexico, Russia, South Africa, and Ukraine and corresponding patent applications in Brazil, Canada, China, Europe, Hong Kong, India, Israel, New Zealand, South Africa, and South Korea, directed to formulations including etripamil, methods of making such formulations, and uses of such formulations to treat angina or cardiac arrhythmias, such as PSVT and atrial fibrillation.

The terms of individual patents may vary based on the countries in which they are obtained. Generally, patents issued for applications filed in the United States are effective for 20 years from the earliest effective non-provisional filing date in the absence, for example, of a terminal disclaimer shortening the term of the patent or patent term adjustment increasing the term of the patent. In addition, in certain instances, a patent term can be extended to recapture a portion of the term effectively lost as a results of FDA regulatory review periods. The restoration period cannot be longer than five years and the total term, including the restoration period, must not exceed 14 years following FDA approval. The duration of patents outside the United States varies in accordance with provisions of applicable local law, but typically is also 20 years from the earliest non-provisional filing date.

In addition to patents and patent applications that we own, we rely on know-how to develop and maintain our competitive position. We seek to protect our proprietary technology and processes, and obtain and maintain ownership of certain technologies, in part, through confidentiality agreements and invention assignment agreements with our employees, consultants, scientific advisors, contractors and commercial partners.

Our future commercial success depends, in part, on our ability to obtain and maintain patent and other proprietary protection for commercially important technology, inventions and know-how related to our business; defend and enforce our patents; and operate without infringing valid enforceable patents and proprietary rights of third parties. Our ability to stop third parties from making, using, selling, offering to sell or importing our products may depend on the extent to which we have rights under valid and enforceable patents that cover these activities. With respect to our owned intellectual property, we cannot be sure that patents will issue from any of the pending patent applications to which we own or from any patent applications that we may file in the future, nor can we be sure that any patents that may be issued in the future to us will be commercially useful in protecting etripamil or any future product candidates and methods of using or manufacturing the same. Moreover, we may be unable to obtain patent protection for certain aspects of etripamil or future product candidates generally, as well as with respect to certain indications. See the section entitled “Risk Factors—Risks Related to Our Intellectual Property” for a more comprehensive description of risks related to our intellectual property.

Government Regulation and Product Approval

Government authorities in the United States, at the federal, state and local levels, and in other countries, extensively regulate, among other things, the research, development, testing, manufacture, packaging, storage, recordkeeping, labeling, advertising, promotion, distribution, marketing, import and export of pharmaceutical products, such as those we are developing. The processes for obtaining regulatory approvals in the United States and in foreign countries, along with subsequent compliance with applicable statutes and regulations, require the expenditure of substantial time and financial resources.

United States Government Regulation

In the United States, the FDA regulates drugs under the Federal Food, Drug, and Cosmetic Act, or FDCA, and its implementing regulations. The process of obtaining regulatory approvals and the subsequent compliance with appropriate federal, state, local and foreign statutes and regulations requires the expenditure of substantial time and financial resources. Failure to comply with the applicable United States requirements at any time during the drug development process, approval process or after approval, may subject an applicant to a variety of administrative or judicial sanctions, such as the FDA’s refusal to approve a pending New Drug Application, or NDA, withdrawal of an approval, imposition of a clinical hold, issuance of warning or untitled letters, product recalls, product seizures, total or

partial suspension of production or distribution, injunctions, fines, refusals of government contracts, restitution, disgorgement or civil or criminal penalties.

The process required by the FDA before a drug may be marketed in the United States generally involves:

- completion of preclinical laboratory tests, animal studies and formulation studies in compliance with the FDA's good laboratory practice, or GLP, regulations;
- submission to the FDA of an IND, which must become effective before human clinical trials may begin;
- approval by an independent institutional review board, or IRB, at each clinical site before each trial may be initiated;
- performance of adequate and well controlled clinical trials, in accordance with good clinical practice, or GCP, requirements to establish the safety and efficacy of the proposed drug for each indication;
- submission to the FDA of an NDA;
- satisfactory completion of an FDA advisory committee review, if applicable;
- satisfactory completion of an FDA inspection of the manufacturing facility or facilities at which the product is produced to assess compliance with cGMP requirements, and to assure that the facilities, methods and controls are adequate to preserve the drug's identity, strength, quality and purity;
- satisfactory completion of an FDA inspection of selected clinical sites to assure compliance with GCPs and the integrity of the clinical data;
- payment of user fees; and
- FDA review and approval of the NDA.

Preclinical Studies

Preclinical studies include laboratory evaluation of product chemistry, toxicity and formulation, as well as animal studies to assess potential safety and efficacy. An IND sponsor must submit the results of the nonclinical tests, together with manufacturing information, analytical data and any available clinical data or literature, among other things, to the FDA as part of an IND. Some nonclinical testing may continue even after the IND is submitted. An IND automatically becomes effective 30 days after receipt by the FDA, unless before that time the FDA raises concerns or questions related to one or more proposed clinical trials and places the clinical trial on a clinical hold.

In such a case, the IND sponsor and the FDA must resolve any outstanding concerns before the clinical trial can begin. As a result, submission of an IND may not result in the FDA allowing clinical trials to commence.

Clinical Trials

Clinical trials involve the administration of the investigational new drug to human subjects under the supervision of qualified investigators in accordance with GCP requirements, which include the requirement that all research subjects provide their informed consent in writing for their participation in any clinical trial. Clinical trials are conducted under protocols detailing, among other things, the objectives of the trial, the parameters to be used in monitoring safety and the effectiveness criteria to be evaluated. A protocol for each clinical trial and any subsequent protocol amendments must be submitted to the FDA as part of the IND. In addition, an IRB at each institution participating in the clinical trial must review and approve the plan for any clinical trial before it commences at that institution, and the IRB must continue to oversee the clinical trial while it is being conducted. Information about certain clinical trials must be submitted within

specific timeframes to the National Institutes of Health, or NIH, for public dissemination on their ClinicalTrials.gov website.

Human clinical trials are typically conducted in three sequential phases, which may overlap or be combined. In Phase 1, the drug is initially introduced into healthy human subjects or patients with the target disease or condition and tested for safety, dosage tolerance, absorption, metabolism, distribution, excretion and, if possible, to gain an initial indication of its effectiveness. In Phase 2, the drug typically is administered to a limited patient population to identify possible adverse effects and safety risks, to preliminarily evaluate the efficacy of the product for specific targeted diseases and to determine dosage tolerance and optimal dosage. In Phase 3, the drug is administered to an expanded patient population, generally at geographically dispersed clinical trial sites, in well controlled clinical trials to generate enough data to statistically evaluate the safety and efficacy of the product for approval, to establish the overall risk benefit profile of the product and to provide adequate information for the labeling of the product.

Progress reports detailing the results of the clinical trials must be submitted, at least annually, to the FDA, and more frequently if serious adverse events occur. Phase 1, Phase 2 and Phase 3 clinical trials may not be completed successfully within any specified period, or at all. Furthermore, the FDA or the sponsor may suspend or terminate a clinical trial at any time on various grounds, including a finding that the research subjects are being exposed to an unacceptable health risk. Similarly, an IRB can suspend or terminate approval of a clinical trial at its institution if the clinical trial is not being conducted in accordance with the IRB's requirements, or if the drug has been associated with unexpected serious harm to patients.

Marketing Approval

Assuming successful completion of the required clinical testing, the results of the preclinical and clinical studies, together with detailed information relating to the product's chemistry, manufacture, controls and proposed labeling, among other things, are submitted to the FDA as part of an NDA requesting approval to market the product for one or more indications. In most cases, the submission of an NDA is subject to a substantial application user fee. Under the Prescription Drug User Fee Act, or PDUFA, guidelines that are currently in effect, the FDA has a goal of ten months from the date of "filing" of a standard NDA for a new molecular entity to review and act on the submission. This review typically takes twelve months from the date the NDA is submitted to the FDA because the FDA has approximately two months to make a "filing" decision.

In addition, under the Pediatric Research Equity Act, certain NDAs or supplements to an NDA must contain data that are adequate 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 product is safe and effective. The FDA may, on its own initiative or at the request of the applicant, grant deferrals for submission of some or all pediatric data until after approval of the product for use in adults, or full or partial waivers from the pediatric data requirements. Unless otherwise required by regulation, the pediatric data requirements do not apply to products with orphan designation.

The FDA also may require submission of a risk evaluation and mitigation strategy, or REMS, plan to ensure that the benefits of the drug outweigh its risks. The REMS plan could include medication guides, physician communication plans, assessment plans, and/or elements to assure safe use, such as restricted distribution methods, patient registries or other risk minimization tools.

The FDA conducts a preliminary review of all NDAs within the first 60 days after submission, before accepting them for filing, to determine whether they are sufficiently complete to permit substantive review. The FDA may request additional information rather than accept an NDA for filing. In this event, the application must be resubmitted with the additional information. The resubmitted application is also subject to review before the FDA accepts it for filing. Once the submission is accepted for filing, the FDA begins an in-depth substantive review. The FDA reviews an NDA to determine, among other things, whether the drug is safe and effective and whether the facility in which it is manufactured, processed, packaged or held meets standards designed to assure the product's continued safety, quality and purity.

The FDA may refer an application for a novel drug to an advisory committee. An advisory committee is a panel of independent experts, including clinicians and other scientific experts, that reviews, evaluates and provides a recommendation as to whether the application should be approved and under what conditions. The FDA is not bound by the recommendations of an advisory committee, but it considers such recommendations carefully when making decisions.

Before approving an NDA, the FDA typically will inspect the facility or facilities where the product is manufactured. The FDA will not approve an application unless it determines that the manufacturing processes and facilities are in compliance with cGMP requirements and adequate to assure consistent production of the product within required specifications. Additionally, before approving an NDA, the FDA will typically inspect one or more clinical trial sites to assure compliance with GCP requirements.

The testing and approval process for an NDA requires substantial time, effort and financial resources, and takes several years to complete. Data obtained from preclinical and clinical testing are not always conclusive and may be susceptible to varying interpretations, which could delay, limit or prevent regulatory approval. The FDA may not grant approval of an NDA on a timely basis, or at all.

After evaluating the NDA and all related information, including the advisory committee recommendation, if any, and inspection reports regarding the manufacturing facilities and clinical trial sites, the FDA may issue an approval letter, or, in some cases, a complete response letter. A complete response letter generally contains a statement of specific conditions that must be met in order to secure final approval of the NDA and may require additional clinical or preclinical testing in order for FDA to reconsider the application. Even with submission of this additional information, the FDA ultimately may decide that the application does not satisfy the regulatory criteria for approval. If and when those conditions have been met to the FDA's satisfaction, the FDA will typically issue an approval letter. An approval letter authorizes commercial marketing of the drug with specific prescribing information for specific indications.

Even if the FDA approves a product, it may limit the approved indications for use of the product, require that contraindications, warnings or precautions be included in the product labeling, require that post-approval studies, including Phase 4 clinical trials, be conducted to further assess a drug's safety after approval, require testing and surveillance programs to monitor the product after commercialization, or impose other conditions, including distribution and use restrictions or other risk management mechanisms under a REMS, which can materially affect the potential market and profitability of the product. The FDA may prevent or limit further marketing of a product based on the results of post-marketing studies or surveillance programs. After approval, some types of changes to the approved product, such as adding new indications, manufacturing changes, and additional labeling claims, are subject to further testing requirements and FDA review and approval.

Special FDA Expedited Review and Approval Programs

The FDA has various programs, including fast track designation, accelerated approval, priority review, and breakthrough therapy designation, which are intended to expedite or simplify the process for the development and FDA review of drugs that are intended for the treatment of serious or life threatening diseases or conditions and demonstrate the potential to address unmet medical needs. The purpose of these programs is to provide important new drugs to patients earlier than under standard FDA review procedures.

To be eligible for a fast track designation, the FDA must determine, based on the request of a sponsor, that a product is intended to treat a serious or life-threatening disease or condition and demonstrates the potential to address an unmet medical need. The FDA will determine that a product will fill an unmet medical need if it will provide a therapy where none exists or provide a therapy that may be potentially superior to existing therapy based on efficacy or safety factors. The FDA may review sections of the NDA for a fast track product on a rolling basis before the complete application is submitted. If the sponsor provides a schedule for the submission of the sections of the NDA, the FDA agrees to accept sections of the NDA and determines that the schedule is acceptable, and the sponsor pays any required user fees upon submission of the first section of the NDA.

The FDA may give a priority review designation to drugs that are designed to treat serious conditions, and if approved, would provide a significant improvement in treatment, or provide a treatment where no adequate therapy exists. A priority review means that the goal for the FDA to review an application is six months, rather than the standard review of ten months under current PDUFA guidelines. Under the current PDUFA agreement, these six and ten month review periods are measured from the "filing" date rather than the receipt date for NDAs for new molecular entities, which typically adds approximately two months to the timeline for review and decision from the date of submission. Most products that are eligible for fast track designation are also likely to be considered appropriate to receive a priority review.

In addition, products studied for their safety and effectiveness in treating serious or life-threatening illnesses and that provide meaningful therapeutic benefit over existing treatments may be eligible for accelerated approval and may be approved on the basis of adequate and well-controlled clinical trials establishing that the drug product has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit, or on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality, that is reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit, taking into account the severity, rarity or prevalence of the condition and the availability or lack of alternative treatments. As a condition of approval, the FDA may require a sponsor of a drug receiving accelerated approval to perform post-marketing studies to verify and describe the predicted effect on irreversible morbidity or mortality or other clinical endpoint, and the drug may be subject to accelerated withdrawal procedures.

Breakthrough therapy designation is for a drug that is intended, alone or in combination with one or more other drugs, to treat a serious or life-threatening disease or condition, and preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development. The FDA must take certain actions, such as holding timely meetings and providing advice, intended to expedite the development and review of an application for approval of a breakthrough therapy.

Even if a product qualifies for one or more of these programs, the FDA may later decide that the product no longer meets the conditions for qualification or decide that the time period for FDA review or approval will not be shortened. We may explore some of these opportunities for our product candidates as appropriate.

Rare pediatric disease designation by the FDA enables priority review voucher, or PRV, eligibility upon U.S. market approval of a designated drug for rare pediatric diseases. The RPD-PRV program is intended to encourage development of therapies to prevent and treat rare pediatric diseases. The voucher, which is awarded upon NDA or BLA approval to the sponsor of a designated RPD can be sold or transferred to another entity and used by the holder to receive priority review for a future NDA or BLA submission, which reduces the FDA review time of such future submission from ten to six months.

Post Approval Requirements

Drugs manufactured or distributed pursuant to FDA approvals are subject to pervasive and continuing regulation by the FDA, including, among other things, requirements relating to recordkeeping, periodic reporting, product sampling and distribution, advertising and promotion and reporting of adverse experiences with the product. After approval, most changes to the approved product, such as adding new indications, manufacturing changes or other labeling claims, are subject to further testing requirements and prior FDA review and approval. There also are continuing annual user fee requirements for any marketed products and the establishments at which such products are manufactured, as well as application fees for supplemental applications with clinical data.

Even if the FDA approves a product, it may limit the approved indications for use of the product, require that contraindications, warnings or precautions be included in the product labeling, including a boxed warning, require that post-approval studies, including Phase 4 clinical trials, be conducted to further assess a drug's safety after approval, require testing and surveillance programs to monitor the product after commercialization, or impose other conditions, including distribution restrictions or other risk management mechanisms under a REMS, which can materially affect the

potential market and profitability of the product. The FDA may prevent or limit further marketing of a product based on the results of post-marketing studies or surveillance programs.

In addition, drug manufacturers and other entities involved in the manufacture and distribution of approved drugs are required to register their establishments with the FDA and state agencies, and are subject to periodic unannounced inspections by the FDA and these state agencies for compliance with cGMP requirements. Changes to the manufacturing process are strictly regulated and often require prior FDA approval before being implemented. FDA regulations also require investigation and correction of any deviations from cGMP and impose reporting and documentation requirements upon the sponsor and any third-party manufacturers that the sponsor may decide to use. Accordingly, manufacturers must continue to expend time, money and effort in the area of production and quality control to maintain cGMP compliance.

Once an approval is granted, the FDA may withdraw the approval if compliance with regulatory requirements and standards is not maintained or if problems occur after the product reaches the market.

Later discovery of previously unknown problems with a product, including adverse events of unanticipated severity or frequency, or with manufacturing processes, or failure to comply with regulatory requirements, may result in mandatory revisions to the approved labeling to add new safety information; imposition of post-market studies or clinical trials to assess new safety risks; or imposition of distribution or other restrictions under a REMS program. Other potential consequences include, among other things:

- restrictions on the marketing or manufacturing of the product, complete withdrawal of the product from the market or product recalls;
- fines, warning letters or holds on post-approval clinical trials;
- refusal of the FDA to approve pending NDAs or supplements to approved NDAs, or suspension or revocation of product approvals;
- product seizure or detention, or refusal to permit the import or export of products; or
- injunctions or the imposition of civil or criminal penalties.

The FDA strictly regulates marketing, labeling, advertising and promotion of products that are placed on the market. Drugs may be promoted only for the approved indications and in accordance with the provisions of the approved label, although physicians, based on their independent medical judgement, may prescribe approved drugs for unapproved indications. However, biopharmaceutical companies may share truthful and not misleading information that is otherwise consistent with the labeling. The FDA and other agencies actively enforce the laws and regulations prohibiting their promotion of off-label uses, and a company that is found to have improperly promoted off-label uses may be subject to significant civil, criminal and administrative liability.

In addition, the distribution of prescription pharmaceutical products is subject to the Prescription Drug Marketing Act, or PDMA, which regulates the distribution of drugs and drug samples at the federal level, and sets minimum standards for the registration and regulation of drug distributors by the states. Both the PDMA and state laws limit the distribution of prescription pharmaceutical product samples and impose requirements to ensure accountability in distribution.

Federal and State Fraud and Abuse, Data Privacy and Security, and Transparency Laws and Regulations

In addition to FDA restrictions on marketing of pharmaceutical products, federal and state healthcare laws and regulations restrict business practices in the biopharmaceutical industry. These laws may impact, among other things, our current and future business operations, including our clinical research activities, and proposed sales, marketing and education programs and constrain the business or financial arrangements and relationships with healthcare providers and other parties through which we market, sell and distribute our products for which we obtain marketing approval. These

laws include anti-kickback and false claims laws and regulations, data privacy and security, and transparency laws and regulations, including, without limitation, those laws described below.

The federal Anti-Kickback Statute prohibits any person or entity from, among other things, knowingly and willfully offering, paying, soliciting or receiving remuneration to induce or in return for purchasing, leasing, ordering or arranging for or recommending the purchase, lease or order of any item or service reimbursable under Medicare, Medicaid or other federal healthcare programs. The term "remuneration" has been broadly interpreted to include anything of value. The federal Anti-Kickback Statute has been interpreted to apply to arrangements between pharmaceutical manufacturers on the one hand and prescribers, purchasers and formulary managers on the other. Although there are a number of statutory exceptions and regulatory safe harbors protecting some common activities from prosecution, the exceptions and safe harbors are drawn narrowly. Practices that involve remuneration that may be alleged to be intended to induce prescribing, purchases or recommendations may be subject to scrutiny if they do not qualify for an exception or safe harbor. Several courts have interpreted the statute's intent requirement to mean that if any one purpose of an arrangement involving remuneration is to induce referrals of federal healthcare covered business, the statute has been violated.

A person or entity does not need to have actual knowledge of this statute or specific intent to violate it in order to have committed a violation. In addition, the government may assert that a claim including items or services resulting from a violation of the federal Anti-Kickback Statute constitutes a false or fraudulent claim for purposes of the federal civil False Claims Act or the civil monetary penalties laws.

Federal civil and criminal false claims laws, including the federal civil False Claims Act, which can be enforced by individuals through civil whistleblower and qui tam actions, and civil monetary penalties laws, prohibits any person or entity from, among other things, knowingly presenting, or causing to be presented, a false claim for payment to the federal government or knowingly making, using or causing to be made or used a false record or statement material to a false or fraudulent claim to the federal government. A claim includes "any request or demand" for money or property presented to the U.S. government. Several pharmaceutical and other healthcare companies have been prosecuted under these laws for allegedly providing free product to customers with the expectation that the customers would bill federal programs for the product. Other companies have been prosecuted for causing false claims to be submitted because of the companies' marketing of products for unapproved, and thus non-reimbursable, uses.

The federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, created additional federal criminal statutes that prohibit, among other things, knowingly and willfully executing a scheme to defraud any healthcare benefit program, including private third-party payors and knowingly and willfully falsifying, concealing or covering up a material fact or making any materially false, fictitious or fraudulent statement in connection with the delivery of or payment for healthcare benefits, items or services. Also, many states have similar fraud and abuse statutes or regulations that apply to items and services reimbursed under Medicaid and other state programs, or, in several states, apply regardless of the payor.

In addition, we may be subject to data privacy and security regulation by both the federal government and the states in which we conduct our business. HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act, or HITECH, and their respective implementing regulations, impose specified requirements on certain types of individuals and entities relating to the privacy, security and transmission of individually identifiable health information. Among other things, HITECH makes HIPAA's security standards directly applicable to "business associates," defined as independent contractors or agents of covered entities, which include certain healthcare providers, healthcare clearinghouse and health plans, that create, receive, maintain or transmit individually identifiable health information in connection with providing a service for or on behalf of a covered entity, and their covered subcontractors. HITECH also increased the civil and criminal penalties that may be imposed against covered entities, business associates and possibly other persons, and gave state attorneys general new authority to file civil actions for damages or injunctions in federal courts to enforce HIPAA and seek attorney's fees and costs associated with pursuing federal civil actions. In addition, state laws govern the privacy and security of health information in certain circumstances, many of which are not pre-empted by HIPAA, differ from each other in significant ways and may not have the same effect, thus complicating compliance efforts.

The federal Physician Payments Sunshine Act requires certain manufacturers of drugs, devices, biologics and medical supplies for which payment is available under Medicare, Medicaid or the Children's Health Insurance Program, with specific exceptions, to report annually to the Centers for Medicare & Medicaid Services, or CMS, information related to payments or other transfers of value made to physicians (defined to include doctors, dentists, optometrists, podiatrists and chiropractors), and teaching hospitals, and applicable manufacturers and applicable group purchasing organizations to report annually to CMS ownership and investment interests held by physicians and their immediate family members. Beginning in 2022, applicable manufacturers also will be required to report such information regarding payments and other transfers of value to physician assistants, nurse practitioners, clinical nurse specialists, anesthesiologist assistants, certified registered nurse anesthetists and certified nurse midwives provided during the previous year.

We may also be subject to state laws that require pharmaceutical companies to comply with the pharmaceutical industry's voluntary compliance guidelines and the relevant compliance guidance promulgated by the federal government, state laws that require drug manufacturers to report information related to payments and other transfers of value to physicians and other healthcare providers or marketing expenditures, state laws that require drug manufacturers to report information on the pricing of certain drugs, and state and local laws that require the registration of pharmaceutical sales representatives.

Because of the breadth of these laws and the narrowness of available statutory exceptions and regulatory safe harbors, it is possible that some of our business activities could be subject to challenge under one or more of such laws. If our operations are found to be in violation of any of the federal and state laws described above or any other governmental regulations that apply to us, we may be subject to significant criminal, civil and administrative penalties including damages, fines, imprisonment, 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, contractual damages, reputational harm, diminished profits and future earnings, disgorgement, exclusion from participation in government healthcare programs and the curtailment or restructuring of our operations, any of which could adversely affect our ability to operate our business and our results of operations. To the extent that any of our products are sold in a foreign country, we may be subject to similar foreign laws and regulations, which may include, for instance, applicable post-marketing requirements, including safety surveillance, anti-fraud and abuse laws, implementation of corporate compliance programs, reporting of payments or transfers of value to healthcare professionals, and additional data privacy and security requirements.

Coverage and Reimbursement

The future commercial success of our, or any of our collaborators', product candidates, if approved, will depend in part on the extent to which third-party payors, such as governmental payor programs at the federal and state levels, including Medicare and Medicaid, private health insurers and other third-party payors, provide coverage of and establish adequate reimbursement levels for our product candidates. Third-party payors generally decide which products they will pay for and establish reimbursement levels for those products. In particular, in the United States, no uniform policy for coverage and reimbursement exists. Private health insurers and other third-party payors often provide coverage and reimbursement for products based on the level at which the government, through the Medicare program, provides coverage and reimbursement for such products, but also have their own methods and approval process apart from Medicare determinations. Therefore, coverage and reimbursement can differ significantly from payor to payor.

In the United States, the European Union, or EU, and other potentially significant markets for our product candidates, government authorities and third-party payors are increasingly attempting to limit or regulate the price of products, particularly for new and innovative products, which often has resulted in average selling prices lower than they would otherwise be. Further, the increased emphasis on managed healthcare in the United States and on country and regional pricing and reimbursement controls in the EU will put additional pressure on product pricing, reimbursement and usage. These pressures can arise from rules and practices of managed care groups, judicial decisions and laws and regulations related to Medicare, Medicaid and healthcare reform, pharmaceutical coverage and reimbursement policies and pricing in general.

Third-party payors are increasingly imposing additional requirements and restrictions on coverage and limiting reimbursement levels for products. For example, federal and state governments reimburse products at varying rates generally below average wholesale price. These restrictions and limitations influence the purchase of products. Third-party payors may limit coverage to specific products on an approved list, or formulary, which might not include all of the FDA-approved products for a particular indication. Third-party payors are increasingly challenging the price and examining the medical necessity and cost-effectiveness of products, in addition to their safety and efficacy. We may need to conduct expensive pharmacoeconomic studies in order to demonstrate the medical necessity and cost-effectiveness of our product candidates, in addition to the costs required to obtain the FDA approvals. Our product candidates may not be considered medically necessary or cost-effective. A payor's decision to provide coverage for a product does not imply that an adequate reimbursement rate will be approved. Adequate third-party payor reimbursement may not be available to enable us to realize an appropriate return on our investment in product development. Legislative proposals to reform healthcare or reduce costs under government insurance programs may result in lower reimbursement for our product candidates, if approved, or exclusion of our product candidates from coverage and reimbursement. The cost containment measures that third-party payors and providers are instituting and any healthcare reform could significantly reduce our revenues from the sale of any approved product candidates.

Healthcare Reform

The United States and some foreign jurisdictions are considering enacting or have enacted a number of additional legislative and regulatory proposals to change the healthcare system in ways that could affect our ability to sell our product candidates profitably, if approved. Among policy makers and payors in the United States and elsewhere, there is significant interest in promoting changes in healthcare systems with the stated goals of containing healthcare costs, improving quality and expanding access. In the United States, the pharmaceutical industry has been a particular focus of these efforts, which include major legislative initiatives to reduce the cost of care through changes in the healthcare system, including limits on the pricing, coverage, and reimbursement of pharmaceutical and biopharmaceutical products, especially under government-funded health care programs, and increased governmental control of drug pricing.

There have been several U.S. government initiatives over the past few years to fund and incentivize certain comparative effectiveness research, including creation of the Patient-Centered Outcomes Research Institute under the Patient Protection and Affordable Care Act of 2010, as amended by the Health Care and Education Reconciliation Act of 2010, or collectively the PPACA. It is also possible that comparative effectiveness research demonstrating benefits in a competitor's product could adversely affect the sales of our product candidates.

The PPACA became law in March 2010 and substantially changed the way healthcare is financed by both third-party payors. Among other measures that may have an impact on our business, the PPACA establishes an annual, nondeductible fee on any entity that manufactures or imports specified branded prescription drugs and biologic agents; a new Medicare Part D coverage gap discount program; and a new formula that increases the rebates a manufacturer must pay under the Medicaid Drug Rebate Program. Additionally, the PPACA extends manufacturers' Medicaid rebate liability, expands eligibility criteria for Medicaid programs, and expands entities eligible for discounts under the Public Health Service Act. At this time, we are unsure of the full impact that the PPACA will have on our business.

There have been executive, judicial and Congressional challenges to certain aspects of the PPACA.While Congress has not passed comprehensive repeal legislation, several bills affecting the implementation of certain taxes under the PPACA have been signed into law. The Tax Cuts and Jobs Act of 2017, or Tax Act, included a provision that repealed, effective January 1, 2019, the tax-based shared responsibility payment imposed by the PPACA on certain individuals who fail to maintain qualifying health coverage for all or part of a year that is commonly referred to as the "individual mandate." In addition, the 2020 federal spending package permanently eliminated, effective January 1, 2020, the PPACA-mandated "Cadillac" tax on high-cost employer-sponsored health coverage and medical device tax and, effective January 1, 2021, also eliminated the health insurer tax. The Bipartisan Budget Act of 2018, or the BBA, among other things, amended the PPACA, effective January 1, 2019, to increase from 50% to 70% the point-of-sale discount that is owed by pharmaceutical manufacturers who participate in Medicare Part D and to close the coverage gap in most Medicare drug plans, commonly referred to as the "donut hole." On December 14, 2018, a Texas U.S. District Court Judge ruled that the PPACA is unconstitutional in its entirety because the "individual mandate" was repealed by Congress as part of the Tax Act. Additionally, on December 18, 2019, the U.S. Court of Appeals for the 5th Circuit

upheld the District Court ruling that the individual mandate was unconstitutional and remanded the case back to the District Court to determine whether the remaining provisions of the PPACA are invalid as well. The United States Supreme Court is currently reviewing this case, but it is unknown when a decision will be reached. Although the U.S. Supreme Court has not yet ruled on the constitutionality of the PPACA, on January 28, 2021, President Biden issued an executive order to initiate a special enrollment period from February 15, 2021 through May 15, 2021 for purposes of obtaining health insurance coverage through the PPACA marketplace. The executive order also instructs certain governmental agencies to review and reconsider their existing policies and rules that limit access to healthcare, including among others, reexamining Medicaid demonstration projects and waiver programs that include work requirements, and policies that create unnecessary barriers to obtaining access to health insurance coverage through Medicaid or the PPACA. It is unclear how the Supreme Court ruling, other such litigation and the healthcare reform measures of the Biden administration will impact the PPACA.

In addition, other legislative changes have been proposed and adopted since the PPACA was enacted. In August 2011, the President signed into law the Budget Control Act of 2011, as amended, which, among other things, included aggregate reductions to Medicare payments to providers of 2% per fiscal year, which began in 2013 and, following passage of subsequent legislation, including the BBA, will continue through 2030 with the exception of a temporary suspension from May 1, 2020 through March 31, 2021 due to the COVID-19 pandemic, unless additional Congressional action is taken. In January 2013, the American Taxpayer Relief Act of 2012 was enacted and, among other things, reduced Medicare payments to several providers and increased the statute of limitations period for the government to recover overpayments to providers from three to five years.

Further, there has been increasing legislative and enforcement interest in the United States with respect to drug pricing practices. Specifically, there have been 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, and reform government program reimbursement methodologies for drugs. At the federal level, the Trump administration used several means to propose or implement drug pricing reform, including through federal budget proposals, executive orders and policy initiatives. For example, on July 24, 2020 and September 13, 2020, the Trump administration announced several executive orders related to prescription drug pricing that attempted to implement several of the administration’s proposals. As a result, the FDA also released a final rule on September 24, 2020, effective November 30, 2020, implementing a portion of the importation executive order providing guidance for states to build and submit importation plans for drugs from Canada. Further, on November 20, 2020, HHS finalized a regulation removing safe harbor protection for price reductions from pharmaceutical manufacturers to plan sponsors under Part D, either directly or through pharmacy benefit managers, unless the price reduction is required by law. The implementation of the rule has been delayed by the Biden administration from January 1, 2022 to January 1, 2023 in response to ongoing litigation. The rule also creates a new safe harbor for price reductions reflected at the point-of-sale, as well as a new safe harbor for certain fixed fee arrangements between pharmacy benefit managers and manufacturers, the implementation of which have also been delayed pending review by the Biden administration until March 22, 2021. On November 20, 2020, CMS issued an interim final rule implementing the Trump administration’s Most Favored Nation executive order, which would tie Medicare Part B payments for certain physician-administered drugs to the lowest price paid in other economically advanced countries, effective January 1, 2021. On December 28, 2020, the United States District Court in Northern California issued a nationwide preliminary injunction against implementation of the interim final rule. It is unclear whether the Biden administration will work to reverse these measures or pursue similar policy initiatives. At the state level, legislatures have increasingly passed legislation and implemented regulations designed to control pharmaceutical and biological 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. It also possible that governmental action will be taken in response to the COVID-19 pandemic..

Foreign Regulation

In order to market any product outside of the United States, we would need to comply with numerous and varying regulatory requirements of other countries regarding safety and efficacy and governing, among other things, clinical trials, marketing authorization, commercial sales and distribution of our product candidates. For example, in the EU, we must obtain authorization of a clinical trial application, or CTA, in each member state in which we intend to conduct a

clinical trial. Whether or not we obtain FDA approval for a drug, we would need to obtain the necessary approvals by the comparable regulatory authorities of foreign countries before we can commence clinical trials or marketing of the drug in those countries. The approval process varies from country to country and can involve additional product testing and additional administrative review periods. The time required to obtain approval in other countries might differ from and be longer than that required to obtain FDA approval. Regulatory approval in one country does not ensure regulatory approval in another, but a failure or delay in obtaining regulatory approval in one country may negatively impact the regulatory process in others.

Employees and Human Capital

Our human capital is integral to helping us achieve our mission of developing innovative cardiovascular medicines. We have built a culture of high performance based on our core values:

- *Patients first:* everything we do is with the patient in mind. We listen to and partner with patients, and we place the patients' well-being at the core of all our initiatives.
- *Teamwork*: only through teamwork, collaboration and mentorship do we achieve our goals of developing innovative medicines for patients.
- *Humility:* acting selflessly by putting the collective mission first.

Our human capital objectives include, as applicable, identifying, recruiting, retaining, incentivizing and integrating our existing and additional employees. The principal purposes of our equity incentive plans are to attract, retain and motivate selected employees, consultants and directors through the granting of stock-based compensation awards.

As of December 31, 2020, we had 28 full-time employees, 13 of whom were primarily engaged in research and development activities and 6 of our employees had an M.D. or Ph.D. degree. None of our employees is represented by a labor union and we consider our employee relations to be good.

Facilities

Our headquarters is currently located in Montréal (Québec), Canada and consists of 7,700 square feet of leased office space under a lease that expires in November 2025 with an option to terminate in November 2023 . We also have a U.S. subsidiary in Charlotte, North Carolina that occupies 5,116 square feet of leased office space under a lease that expires in September 2022. We believe that our facilities are adequate to meet our current needs.

Legal Proceedings

From time to time, we may become involved in legal proceedings arising in the ordinary course of our business. We are not currently a party to any material legal proceedings, and we are not aware of any pending or threatened legal proceeding against us that we believe could have an adverse effect on our business, operating results or financial condition.

Corporate Information

Our principal executive offices are located at 1111 Dr. Frederik-Philips Blvd., Suite 420, Montréal, Québec, Canada H4M 2X6, and our telephone number is (514) 336-0444.

Available Information

We maintain an internet website at www.milestonepharma.com and make available free of charge through our website our Annual Reports on Form 10-K, Quarterly Reports on Form 10-Q, Current Reports on Form 8-K and amendments to those reports filed or furnished pursuant to Sections 13(a) and 15(d) of the Exchange Act of 1934 (the "Exchange Act"). We make these reports available through our website as soon as reasonably practicable after we electronically file such reports with, or furnish such reports to, the Securities and Exchange Commission (the "SEC"). You can review our electronically filed reports and other information that we file with the SEC on the SEC's web site at http://www.sec.gov. We also make available, free of charge on our website, the reports filed with the SEC by our executive officers, directors

and 10% stockholders pursuant to Section 16 under the Exchange Act as soon as reasonably practicable after copies of those filings are provided to us by those persons. In addition, we regularly use our website to post information regarding our business, product development programs and governance, and we encourage investors to use our website, particularly the information in the section entitled “Investors,” as a source of information about us.

The information on our website is not incorporated by reference into this Annual Report on Form 10-K and should not be considered to be a part of this Annual Report on Form 10-K. Our website address is included in this Annual Report on Form 10-K as an inactive technical reference only.

Investors and others should note that we announce material information to our investors using one or more of the following: SEC filings, press releases and our corporate website, including without limitation the “Investors” and “Events and Presentations” sections of our website. We use these channels, as well as social media channels such as LinkedIn, in order to achieve broad, non-exclusionary distribution of information to the public and for complying with our disclosure obligations under Regulation FD. It is possible that the information we post on our corporate website or other social media could be deemed to be material information. Therefore, we encourage investors, the media, and others interested in our company to review the information we post on the “Investors” and “Events and Presentations” sections of our corporate website and on our social media channels. The contents of our corporate website and social media channels are not, however, a part of this Annual Report.

ITEM 1A. RISK FACTORS

An investment in shares of our common shares involves a high degree of risk. You should carefully consider the following information about these risks, together with the other information appearing elsewhere in this Annual Report on Form 10-K, consolidated financial statements and related notes thereto and "Management's Discussion and Analysis of Financial Condition and Results of Operations, "before deciding to invest in our common shares. The occurrence of any of the following risks could have a material adverse effect on our business, financial condition, results of operations and future growth prospects or cause our actual results to differ materially from those contained in forward-looking statements we have made in this report and those we may make from time to time. In these circumstances, the market price of our common shares could decline, and you may lose all or part of your investment. We cannot assure you that any of the events discussed below will not occur. Such risks may be amplified by the COVID-19 pandemic and its potential impact on our business and the global economy.

Risks Related to Our Financial Position and Capital Needs

We have incurred significant operating losses since inception and anticipate that we will continue to incur substantial operating losses for the foreseeable future and may never achieve or maintain profitability.

Since inception in 2003, we have incurred significant operating losses. Our net loss was $50.0 million and $55.2 million for the years ended December 31, 2020 and 2019, respectively. As of December 31, 2020, we had an accumulated deficit of $163.5 million We expect to continue to incur significant expenses and increasing operating losses for the foreseeable future. Since inception, we have devoted substantially all of our efforts to research and preclinical and clinical development of etripamil, as well as to expanding our management team and infrastructure. It could be several years, if ever, before we have a commercialized drug. The COVID-19 pandemic has had an impact on our business, operations and clinical development timelines. Government orders and restrictions in order to control the spread of the disease have impacted patient recruitment, enrollment and follow-up visits at clinical sites. At the date of the publication of this annual report, it is not possible to reliably estimate the length and severity of these developments. We expect that our existing cash, cash equivalents and short-term investments to be sufficient to fund our operations under our current operating plan.

The net losses we incur may fluctuate significantly from quarter to quarter and year to year. We anticipate that our expenses will increase substantially if, and as, we:

- continue our ongoing and planned development of etripamil, including our Phase 3 clinical trials of etripamil for the treatment of paroxysmal supraventricular tachycardia, or PSVT, and our ongoing Phase 2 clinical trial of etripamil for the treatment of atrial fibrillation and rapid ventricular rate, or AFib-RVR;
- seek marketing approvals for etripamil for the treatment of PSVT and other cardiovascular indications and any future product candidates that successfully complete clinical trials;
- establish a sales, marketing, manufacturing and distribution capability, either directly or indirectly with third parties, to commercialize etripamil or any future product candidate for which we may obtain marketing approval;
- build a portfolio of product candidates through development, or the acquisition or in-license of drugs, product candidates or technologies;
- initiate preclinical studies and clinical trials for etripamil for any additional indications we may pursue, and for any additional product candidates that we may pursue in the future;
- maintain, protect and expand our intellectual property portfolio;
- hire additional clinical, regulatory and scientific personnel;

- add operational, financial and management information systems and personnel, including personnel to support our product development and planned future commercialization efforts; and

- incur additional legal, insurance related, accounting and other expenses associated with operating as a public company.

To become and remain profitable, we must succeed in developing and eventually commercializing drugs that generate significant revenue. This will require us to be successful in a range of challenging activities, including completing clinical trials of etripamil and any future product candidates that way may pursue, obtaining regulatory approval, procuring commercial-scale manufacturing, marketing and selling etripamil and any future products for which we may obtain regulatory approval, as well as discovering or acquiring and then developing additional product candidates. We are only in the preliminary stages of some of these activities, and we have recently encountered setbacks in our clinical development program for etripamil, as our NODE-301 trial did not meet its primary endpoint. We may never succeed in these activities and, even if we do, may never generate revenues that are significant enough to achieve profitability.

Because of the numerous risks and uncertainties associated with drug development, we are unable to accurately predict the timing or amount of expenses or when, or if, we will be able to achieve profitability.

Our expenses could increase beyond our expectations if we are required by the U.S. Food and Drug Administration, or FDA, the European Medicines Agency or other regulatory authorities to perform studies in addition to those we currently expect, or if there are any delays in the initiation and completion of our clinical trials or the development of etripamil or any future product candidates.

Even if we do achieve profitability, we may not be able to sustain or increase profitability on a quarterly or annual basis. Our failure to become and remain profitable would decrease the value of our company and could impair our ability to raise capital, maintain our research and development efforts, expand our business or continue our operations. A decline in the value of our common shares could also cause you to lose all or part of your investment.

Our limited operating history may make it difficult for you to evaluate the success of our business to date and to assess our future viability.

We are a clinical-stage company founded in 2003, and our operations to date have been largely focused on raising capital, organizing, staffing our company and undertaking preclinical studies and conducting clinical trials for etripamil. As an organization, we have not yet demonstrated an ability to successfully complete clinical development, obtain regulatory approvals, manufacture a commercial-scale product or arrange for a third party to do so on our behalf, or conduct sales and marketing activities necessary for successful commercialization. Consequently, any predictions about our future success or viability may not be as accurate as they could be if we had a longer operating history or a history of successful clinical development and commercialization of products.

We may encounter unforeseen expenses, difficulties, complications, delays and other known or unknown factors in achieving our business objectives. We will need to transition at some point from a company with a research and development focus to a company capable of supporting commercial activities. We may not be successful in such a transition.

Additionally, we expect our financial condition and operating results to continue to fluctuate from quarter to quarter and year to year due to a variety of factors, many of which are beyond our control. Accordingly, you should not rely upon the results of any quarterly or annual periods as indications of future operating performance.

We will require substantial additional funding to finance our operations. If we are unable to raise capital when needed, we could be forced to delay, reduce or terminate our development of etripamil or other operations.

Based on our research and development plans, we expect that our existing cash, cash equivalents and short-term investments, will be sufficient to fund our operations for at least the next 12 months. However, we will need to obtain

substantial additional funding in connection with our continuing operations and planned activities. Our future capital requirements will depend on many factors, including:

- the timing, progress and results of our ongoing and planned clinical trials of etripamil in PSVT, AFib-RVR and in other cardiovascular indications;
- the scope, progress, results and costs of preclinical development, laboratory testing and clinical trials of etripamil for additional indications or any future product candidates that we may pursue;
- our ability to establish collaborations on favorable terms, if at all;
- the ability of vendors who we rely on to accurately forecast expenses and deliver on expectations;
- the costs, timing and outcome of regulatory review of etripamil and any future product candidates;
- the costs and timing of future commercialization activities, including product manufacturing, marketing, sales and distribution, for etripamil and any future product candidates for which we receive marketing approval;
- the revenue, if any, received from commercial sales of etripamil and any future product candidates for which we receive marketing approval;
- the costs and timing of preparing, filing and prosecuting patent applications, maintaining and enforcing our intellectual property rights and defending any intellectual property-related claims;
- the extent to which we acquire or in-license other product candidates and technologies; and
- the costs of operating as a public company.

Identifying potential product candidates and conducting preclinical testing and clinical trials 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. For example, we recently announced that the pivotal NODE-301 trial of etripamil for PSVT did not meet its primary endpoint. There can be no guarantee that the RAPID trial or our clinical trial of etripamil for AFib-RVR will meet their primary endpoints. In addition, etripamil and any future product candidates, if approved, may not achieve commercial success. Our commercial revenues, if any, will be derived from sales of drugs that we do not expect to be commercially available for several years, if at all. 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 on acceptable terms, or at all. 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. If we are unable to raise capital when needed or on attractive terms, we could be forced to delay, reduce or altogether terminate our research and development programs or future commercialization efforts.

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

Until such time, if ever, as we can generate substantial product revenue, we expect to finance our cash needs through public or private equity or debt financings, third-party funding, marketing and distribution arrangements, as well as other collaborations, strategic alliances and licensing arrangements, or any combination of these approaches. We do not have any committed external source of funds. To the extent that we raise additional capital through the sale of equity or convertible debt securities, your ownership interest may be diluted, and the terms of these securities may include liquidation or other preferences that adversely affect your rights as a shareholder. Debt and equity financings, if available, may involve agreements that include covenants limiting or restricting our ability to take specific actions, such

as redeeming our shares, making investments, incurring additional debt, making capital expenditures, declaring dividends or placing limitations on our ability to acquire, sell or license intellectual property rights.

If we raise additional capital through future collaborations, strategic alliances or third-party licensing arrangements, we may have to relinquish valuable rights to our intellectual property, future revenue streams, research programs or product candidates, or grant licenses on terms that may not be favorable to us. If we are unable to raise additional capital when needed, we may be required to delay, limit, reduce or terminate our drug development or future commercialization efforts, or grant rights to develop and market product candidates that we would otherwise develop and market ourselves.

Limited directors' and officers', or D&O insurance, may reduce the amount of money available to us and may make it difficult for us to retain and attract talented and skilled directors and officers.

Due to recent increases in D&O insurance premiums, we have recently reduced coverage under our D&O insurance policy. Under our current policy, our directors, officers and other agents are insured against losses for actions taken in their capacities as directors, officers or agents only if we cannot or are prohibited from indemnifying them for such losses. As a result, we would have to self-fund any indemnification amounts owed to our directors, officers and agents, in which case our financial condition could be materially adversely affected.

We expect that D&O insurance premiums may increase in the future. If the costs of maintaining adequate D&O insurance coverage increase significantly in the future, our financial condition could be materially adversely affected. Additionally, limited D&O insurance, or the perception that our D&O insurance is inadequate, may make it difficult for us to retain and attract talented and skilled directors and officers to serve our company, which could adversely affect our business.

Our ability to use our non-capital loss carryforwards to offset future taxable income may be subject to certain limitations.

In general, where control of a corporation has been acquired by a person or group of persons, subsection 111(5) of the Income Tax Act (Canada), or the Canadian Tax Act, and equivalent provincial income tax legislation restrict the corporation's ability to carry forward non-capital losses from preceding taxation years. We have not performed a detailed analysis to determine whether an acquisition of control for the purposes of subsection 111(5) of the Canadian Tax Act has occurred after each of our previous issuances of common shares or preferred shares. In addition, if we undergo an acquisition of control, our ability to utilize non-capital losses could be limited by subsection 111(5) of the Canadian Tax Act. As of December 31, 2020, we had Canadian federal and provincial non-capital loss carry forwards of $123.5 million and $122.8 million, respectively, which expire beginning in 2027 through 2040. In addition, we also have scientific research and experimental development expenditures of $13.7 million and $16.2 million, respectively, for Canadian federal and provincial income tax purposes, which have not been deducted. These expenditures are available to reduce future taxable income and have an unlimited carry-forward period. Research and development tax credits and expenditures are subject to verification by the tax authorities, and, accordingly, these amounts may vary. Future changes in our share ownership, some of which are outside of our control, could result in an acquisition of control for the purposes of subsection 111(5) of the Canadian Tax Act. Furthermore, our ability to utilize non-capital losses (or U.S. equivalents) of companies that we may acquire in the future may be subject to limitations. As a result, even if we attain profitability, we may be unable to use a material portion of our non-capital losses and other tax attributes, which could negatively impact our future cash flows.

Our subsidiary's ability to use its U.S. net operating loss carryforwards and certain other tax attributes for U.S. income tax purposes may be limited.

As of December 31, 2020, we had U.S. federal net operating loss carryforwards, or NOLs, of $17.4 million as a result of expenses incurred by Milestone Pharmaceuticals USA, Inc., our wholly-owned subsidiary. Under U.S. federal income tax legislation enacted in 2017, informally titled the Tax Cuts and Jobs Act, or the Tax Act, which was modified by legislation enacted on March 27, 2020 entitled the Coronavirus Aid, Relief, and Economic Security Act, or the CARES Act, U.S. federal NOLs incurred in taxable years ending beginning after December 31, 2017 may be carried forward

indefinitely. However, the deductibility of such NOLs in taxable years beginning after December 31, 2020 is limited to 80% of taxable income. It is uncertain if and to what extent various states will conform to the Tax Act or the CARES Act and there may be periods during which the use of NOLs is suspended or otherwise limited at the state level. In addition, under Sections 382 and 383 of the Internal Revenue Code of 1986, as amended, and corresponding provisions of state law, if a corporation undergoes an "ownership change," which is generally defined as a greater than 50% change (by value) in its equity ownership over a three-year period, the corporation's ability to use its pre-change NOL carryforwards and other pre-change tax attributes (such as research tax credits) to offset its post-change income may be limited. It is possible that we have experienced one or more ownership changes in the past. In addition, we may also experience ownership changes in the future as a result of subsequent shifts in our share ownership some of which may be outside of our control. As a result, if we earn net taxable income, our ability to use our pre-ownership change NOL carryforwards to offset U.S. federal taxable income may be subject to limitations, which could potentially result in increased future tax liability to us. In addition, at the state level, there may be periods during which the use of NOLs is suspended or otherwise limited, which could accelerate or permanently increase state taxes owed.

Risks Related to the Development of Our Product Candidates

We have only one product candidate, etripamil, for which we are currently pursuing clinical development. Our future success is substantially dependent on the successful clinical development and regulatory approval of etripamil. If we are not able to obtain required regulatory approvals for etripamil or any future product candidates, we will not be able to commercialize etripamil or any future product candidates and our ability to generate revenue will be adversely affected.

Etripamil is currently our only product candidate. We have not obtained regulatory approval for etripamil or any product candidate, and it is possible that neither etripamil nor any product candidates we may seek to develop in the future will ever obtain regulatory approval. Neither we nor any future collaborator is permitted to market any drug product candidates in the United States or other countries until we receive regulatory approval from the FDA or applicable foreign regulatory agency. The time required to obtain approval or other marketing authorizations by the FDA and comparable foreign regulatory authorities is unpredictable but typically takes many years following the commencement of clinical trials and depends upon numerous factors, including the substantial discretion of the regulatory authorities. In addition, approval policies, regulations or the type and amount of clinical data necessary to gain approval may change during the course of a product candidate's clinical development and may vary among jurisdictions. For example, in July 2020, we announced that the FDA indicated that two studies, the RAPID study and the completed NODE-301 study, could potentially fulfill the efficacy requirement for our NDA for etripamil in patients with PSVT. We proposed certain program changes to the FDA and they agreed.

Prior to obtaining approval to commercialize etripamil and any other drug product candidate in the United States or elsewhere, we must demonstrate with substantial evidence from 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. Results from nonclinical studies and clinical trials can be interpreted in different ways. 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 other regulatory authorities. The FDA may also require us to conduct additional nonclinical studies, including human factor studies, or clinical trials for our product candidates either prior to or post-approval, or it may object to elements of our clinical development program. In addition, the FDA typically refers applications for novel drugs, like etripamil and potentially any future product candidates, to an advisory committee composed of outside experts. The FDA is not bound by the recommendation of the advisory committee, but it considers such recommendation when making its decision.

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

We have invested a significant portion of our time and financial resources in the development of etripamil. Our business is dependent on our ability to successfully complete development of, obtain regulatory approval for, and, if approved, successfully commercialize etripamil and any future product candidates in a timely manner.

Even if we eventually complete clinical testing and receive approval of a new drug application, or NDA, or foreign marketing application for etripamil and any future product candidates, the FDA or the comparable foreign regulatory authorities may grant approval or other marketing authorization contingent on the performance of costly additional clinical trials, including post-market clinical trials. The FDA or the comparable foreign regulatory authorities also may approve or authorize for marketing a product candidate for a more limited indication or patient population that we originally request, and the FDA or comparable foreign regulatory authorities may not approve or authorize the labeling that we believe is necessary or desirable for the successful commercialization of a product candidate. Any delay in obtaining, or inability to obtain, applicable regulatory approval or other marketing authorization would delay or prevent commercialization of that product candidate and would materially adversely impact our business and prospects.

In addition, the FDA and comparable foreign regulatory authorities may change their policies, adopt additional regulations or revise existing regulations or take other actions, which may prevent or delay approval of our future products under development on a timely basis. Such policy or regulatory changes could impose additional requirements upon us that could delay our ability to obtain approvals, increase the costs of compliance or restrict our ability to maintain any marketing authorizations we may have obtained.

We may not be successful in our efforts to expand our pipeline of product candidates beyond etripamil for PSVT.

We intend to build a pipeline of product candidates beyond etripamil for PSVT and progress these product candidates through clinical development. For example, we recently began enrollment in a Phase 2 clinical trial of etripamil for the treatment of AFib-RVR. We may not be able to successfully expand the scope of cardiovascular indications for etripamil beyond PSVT, or leverage our expertise and experience with etripamil in PSVT to other product candidates. We may not be able to in-license, acquire or develop future product candidates that are safe and effective. Even if we are successful in continuing to expand etripamil to other indications and further build our pipeline, the potential product candidates that we identify may not be suitable for clinical development, including as a result of safety, tolerability, efficacy or other characteristics that indicate that they are unlikely to be drugs that will receive marketing approval, achieve market acceptance or obtain reimbursements from third-party payors. If we do not successfully execute on our strategy of expanding our product pipeline, it could significantly harm our financial position and adversely affect the trading price of our common shares.

The development of additional product candidates is risky and uncertain.

Efforts to identify, acquire or in-license, and then develop product candidates require substantial technical, financial and human resources, whether or not any product candidates are ultimately identified. Our efforts may initially show promise in identifying potential product candidates, yet fail to yield product candidates for clinical development, approved products or commercial revenues for many reasons, including the following:

- the methodology used may not be successful in identifying potential product candidates;
- competitors may develop alternatives that render any product candidates we develop obsolete;
- any product candidates we develop may nevertheless be covered by third parties' patents or other exclusive rights;
- a product candidate may be shown to have harmful side effects or other characteristics that indicate it is unlikely to be effective or otherwise does not meet applicable regulatory criteria;
- a product candidate may not be capable of being produced in commercial quantities at an acceptable cost, or at all; and

- a product candidate may not be accepted as safe and effective by physicians, patients, the medical community or third-party payors.

We have limited financial and management resources and, as a result, we may forego or delay pursuit of opportunities with other product candidates or for other indications that later prove to have greater market potential. Our resource allocation decisions may cause us to fail to capitalize on viable commercial drugs or profitable market opportunities. 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 collaboration, licensing or other royalty arrangements in circumstances under which it would have been more advantageous for us to retain sole development and commercialization rights to such product candidate. If we are unsuccessful in identifying and developing additional product candidates or are unable to do so, our business may be harmed.

Success in preclinical studies or earlier clinical trials may not be indicative of results in future clinical trials and we cannot assure you that any ongoing, planned or future clinical trials will lead to results sufficient for the necessary regulatory approvals.

Success in preclinical testing and earlier clinical trials does not ensure that later clinical trials will generate the same results or otherwise provide adequate data to demonstrate the efficacy and safety of a product candidate. Preclinical tests and Phase 1 and Phase 2 clinical trials are primarily designed to test safety, to study pharmacokinetics and pharmacodynamics and to understand the side effects of product candidates at various doses and schedules. Success in preclinical studies and earlier clinical trials does not ensure that later efficacy trials will be successful, nor does it predict final results. For example, our Phase 2 clinical trial of etripamil for PSVT was conducted in an electrophysiology lab, a controlled setting, in which episodes of supraventricular tachycardia, or SVT, were induced and etripamil was administered by healthcare providers. Our Phase 3 clinical trials are being conducted in an at-home setting with patients self-administering etripamil and monitoring their cardiac activity as episodes of SVT occur. Additionally, in our Phase 2 clinical trial, four sprays of study drug were dispensed to patients using four separate FDA approved single spray devices. In our Phase 3 clinical trials, patients self-administer two to four sprays of study drug from an FDA approved device that is capable of delivering two separate sprays. Accordingly, the results of our Phase 2 trial of etripamil may not be replicated in the at-home setting of our Phase 3 clinical trials, and notably, our NODE-301 clinical trial did not meet its primary endpoint. Etripamil and any future product candidates may fail to show the desired safety and efficacy in clinical development despite positive results in preclinical studies or having successfully advanced through earlier clinical trials.

In addition, the design of a clinical trial can determine whether its results will support approval of a product, and flaws in the design of a clinical trial may not become apparent until the clinical trial is well advanced. Clinical trial design flaws are more likely in therapy areas, such as PSVT, where there are limited previous trials from which to learn and model clinical trials. As an organization, we have limited experience designing clinical trials and may be unable to design and execute a clinical trial to support regulatory approval. Many companies in the pharmaceutical and biotechnology industries have suffered significant setbacks in late-stage clinical trials even after achieving promising results in preclinical testing and earlier clinical trials. Data obtained from preclinical and clinical activities are subject to varying interpretations, which may delay, limit or prevent regulatory approval. In addition, we may experience regulatory delays or rejections as a result of many factors, including changes in regulatory policy during the period of our product candidate development. Any such delays could negatively impact our business, financial condition, results of operations and prospects.

Our business, operations and clinical development timelines and plans have been adversely affected by the effects of health epidemics, including the COVID-19 pandemic, and could be affected by future health epidemics.

Our business, operations and clinical development timelines and plans have been, and could in the future be adversely affected by health epidemics in regions where we have concentrations of clinical trial sites or other business operations, and could cause significant disruption in the operations of CROs and manufacturers upon whom we rely.

In response to the evolving COVID-19 pandemic, many state, local and foreign governments put in place quarantines, executive orders, shelter-in-place orders and similar government orders and restrictions in order to control the spread of

the disease which resulted in business closures, work stoppages, slowdowns and delays, work-from-home policies, travel restrictions and cancellation of events. We implemented a work-from-home policy for all employees,[which are still in effect,]and we may take further actions that alter our operations as may be required by federal, state or local authorities, or which we determine are in the best interests of our employees. While the situation is evolving, and certain locations are doing phased re-openings, new restrictions could be implemented, or prior restrictions reinstated in order to address the spread of COVID-19. These actions, and the uncertainty about the ever evolving landscape, could negatively impact productivity and disrupt our business and operations.

Moreover, our clinical development timelines and plans have been and could continue to be affected by the COVID-19 pandemic. We rely on contract research organizations or other third parties to assist us with clinical trials, and we cannot guarantee that they will continue to perform their contractual duties in a timely and satisfactory manner as a result of the COVID-19 pandemic. Clinical trial site initiations and patient enrollment have been and may be further delayed or suspended due to the desire to protect potential study patients and study personnel. For example, some sites for our NODE-303 and RAPID studies have closed their practices to further enrollment at this time. Furthermore, the initiation of enrollment in our Phase 2 clinical trial of etripamil for the treatment of AFib-RVR has been delayed due to closures of clinical trial sites. In addition, already-enrolled patients may not be able to comply with clinical trial protocols or attend follow up visits if quarantines impede patient movement or interrupt healthcare services. Similarly, our ability to recruit and retain patients and principal investigators and site staff who, as healthcare providers, may have heightened exposure to COVID-19 could be adversely impacted. As a result, we may face delays in meeting the anticipated timelines for our ongoing and planned clinical trials.

Further, if the business operations of our third-party manufacturers and suppliers are interrupted, this could disrupt our supply chain and impact our ongoing preclinical studies and clinical trials. In addition, disruptions or delays in chemistry, manufacturing and control activities for current or future product candidates in general may result in delays and challenges in numerous areas of the drug development lifecycle, including preclinical drug development, clinical stage validation and testing and manufacturing.

In addition, the spread of COVID-19, which has caused a broad impact globally, may materially affect us economically. While the potential economic impact brought by and the duration of COVID-19 may be difficult to assess or predict, a widespread pandemic could result in significant disruption of global financial markets, reducing our ability to access capital, which could in the future negatively affect our liquidity. In addition, further recessions or market correction resulting from the spread of COVID-19 could materially affect our business and the value of our common shares.

The global COVID-19 pandemic continues to rapidly evolve, and we will continue to monitor the COVID-19 situation closely. The ultimate impact of the COVID-19 pandemic or a similar health epidemic is highly uncertain and subject to change. We do not yet know the full extent of the potential impacts on our business, our clinical trials, healthcare systems or the global economy as a whole.

We may encounter substantial delays or difficulties in our clinical trials.

We may not commercialize, market, promote or sell any product candidate without obtaining marketing approval from the FDA or comparable foreign regulatory authorities, and we may never receive such approvals. It is impossible to predict when or if any of our product candidates will prove effective or safe in humans and will receive regulatory approval. Before obtaining marketing approval from regulatory authorities for the sale of our product candidates, we must complete preclinical development and then conduct extensive clinical trials to demonstrate the safety and efficacy of our product candidates in humans. Clinical testing is expensive, difficult to design and implement, can take many years to complete and is uncertain as to outcome. A failure of one or more clinical trials can occur at any stage of testing. For example, in March 2020, we reported that the first our NODE-301 trial did not meet its primary endpoint. With agreement from the FDA, we have revised the second part, and renamed it the RAPID trial, but there can be no guarantee that the recently initiated RAPID trial will meet its primary endpoints. Moreover, preclinical and clinical data are often susceptible to varying interpretations and analyses, and many companies that have believed their product candidates performed satisfactorily in preclinical studies and clinical trials have nonetheless failed to obtain marketing approval of their products.

We may experience numerous unforeseen events prior to, during, or as a result of, clinical trials that could delay or prevent our ability to receive marketing approval or commercialize etripamil and any future product candidates, including:

- delays in reaching a consensus with regulatory authorities on design or implementation of our clinical trials;
- regulators or institutional review boards, or IRBs, may not authorize us or our investigators to commence a clinical trial or conduct a clinical trial at a prospective trial site;
- delays in reaching agreement on acceptable terms with prospective clinical research organizations, or CROs, and clinical trial sites;
- the number of patients required for clinical trials of our product candidates may be larger than we anticipate, enrollment in these clinical trials may be slower than we anticipate, patients may drop out of these clinical trials at a higher rate than we anticipate or fail to return for post-treatment follow-up or we may fail to recruit suitable patients to participate in a trial;
- clinical trials of our product candidates may produce negative or inconclusive results;
- imposition of a clinical hold by regulatory authorities as a result of a serious adverse event, concerns with a class of product candidates or after an inspection of our clinical trial operations, trial sites or manufacturing facilities;
- occurrence of serious adverse events associated with the product candidate that are viewed to outweigh its potential benefits;
- changes in regulatory requirements and guidance that require amending or submitting new clinical protocols;
- interruptions resulting from public health emergencies, including those related to the COVID-19 pandemic; or
- we may decide, or regulators may require us, to conduct additional clinical trials or abandon product development programs.

Any inability to successfully complete preclinical and clinical development could result in additional costs to us or impair our ability to generate revenue from future drug sales or other sources. In addition, if we make manufacturing or formulation changes to our product candidates, we may need to conduct additional testing to bridge our modified product candidate to earlier versions. Clinical trial delays could also shorten any periods during which we may have the exclusive right to commercialize our product candidates, if approved, or allow our competitors to bring competing drugs to market before we do, which could impair our ability to successfully commercialize our product candidates and may harm our business, financial condition, results of operations and prospects.

Additionally, if the results of our clinical trials are inconclusive or if there are safety concerns or serious adverse events associated with our product candidates, we may:

- be delayed in obtaining marketing approval, if at all;
- obtain approval for indications or patient populations that are not as broad as intended or desired;
- obtain approval with labeling that includes significant use or distribution restrictions or safety warnings;

- be subject to additional post-marketing testing requirements;
- be required to perform additional clinical trials to support approval or be subject to additional post-marketing testing requirements;
- have regulatory authorities withdraw, or suspend, their approval of the drug or impose restrictions on its distribution in the form of a modified risk evaluation and mitigation strategy, or REMS;
- be subject to the addition of labeling statements, such as warnings or contraindications;
- be sued; or
- experience damage to our reputation.

Our product development costs will also increase if we experience delays in testing or obtaining marketing approvals. We do not know whether any of our preclinical studies or clinical trials will begin as planned, need to be restructured or be completed on schedule, if at all.

Further, we, the FDA or an IRB may suspend our clinical trials at any time if it appears that we or our collaborators are failing to conduct a trial in accordance with regulatory requirements, including the FDA's current Good Clinical Practice, or GCP, regulations, that we are exposing participants to unacceptable health risks, or if the FDA finds deficiencies in our investigational new drug applications, or INDs, or the conduct of these trials. Therefore, we cannot predict with any certainty the schedule for commencement and completion of future clinical trials. If we experience delays in the commencement or completion of our clinical trials, or if we terminate a clinical trial prior to completion, the commercial prospects of our product candidates could be negatively impacted, and our ability to generate revenues from our product candidates may be delayed.

Clinical trials are very expensive, time consuming and difficult to design and implement.

Our product candidates will require clinical testing before we are prepared to submit an NDA, or comparable application to foreign regulatory authorities, for regulatory approval. We cannot predict with any certainty if or when we might submit an application for regulatory approval for any of our product candidates or whether any such application will be approved by the FDA or foreign regulatory authority. Human clinical trials are very expensive and difficult to design and implement, in part because they are subject to rigorous regulatory requirements. For instance, the FDA or foreign regulatory authority may not agree with our proposed endpoints for any future clinical trial of our product candidates, which may delay the commencement of our clinical trials. In addition, we may not succeed in developing and validating disease relevant clinical endpoints based on insights regarding biological pathways for the diseases we are studying. The clinical trial process is also time consuming. We estimate that the successful completion of clinical trials for etripamil and any future product candidates will take several years to complete. Furthermore, failure can occur at any stage, and we could encounter problems that cause us to abandon or repeat clinical trials. For example, t the pivotal NODE-301 trial of etripamil for PSVT did not meet its primary endpoint. As a result, we were required to submit a protocol amendment to the FDA for the RAPID trial.

Enrollment and retention of patients in clinical trials is an expensive and time-consuming process and could be delayed, made more difficult or rendered impossible by multiple factors outside our control.

Identifying and qualifying patients to participate in our clinical trials is critical to our success. If the actual number of patients with PSVT, AFib-RVR or any other indications that we may pursue for etripamil or future product candidates, is smaller than we anticipate, we may encounter difficulties in enrolling patients in our clinical trials, thereby delaying or preventing development and approval of etripamil and any future product candidates. Even once enrolled we may be unable to retain a sufficient number of patients to complete any of our trials. Patient enrollment and retention in clinical trials depends on many factors, including the size of the patient population, the nature of the trial protocol, the existing body of safety and efficacy data, the number and nature of competing treatments and ongoing clinical trials of competing

therapies for the same indication, the proximity of patients to clinical sites, the experience and capabilities of the clinical sites to recruit the correct patients, and the eligibility criteria for the trial. In our Phase 3 clinical trials, we are attempting to enroll elderly patients and patients taking concomitant medications that impact the heart, such as other calcium channel blockers and beta blockers. We are doing this in order to obtain efficacy and safety data on patients representing the subset of our intended population that is most vulnerable to safety concerns with the use of etripamil. Such patients may be difficult to enroll in this trial, and the lack of data on these patients may negatively impact the approvability or labeling of etripamil. Patient enrollment may also continue to be affected by the ongoing COVID-19 pandemic, which could be due to the prioritization of hospitalization resources toward this pandemic, exposure of healthcare providers to COVID-19 and difficulties for patients to access clinical trial sites and comply with clinical trial protocols. For example, some sites for our NODE-303 study have closed their practices to further enrollment.

In our Phase 2 clinical trial of etripamil for the treatment of PSVT, only 104 of 199 enrolled patients completed the trials, with 70 patients unable to induce or sustain episodes of SVT during the trial period. The first Phase 3 trial of PSVT for etripamil enrolled over 400 diagnosed PSVT patients meeting inclusion and exclusion criteria in order to achieve the required treatment of 150 confirmed PSVT episodes. PSVT is episodic and unpredictable, and all of our Phase 3 trial designs depend on patients experiencing and recognizing an episode of SVT, self-administering etripamil and monitoring their cardiac activity using a monitoring device. We cannot control the timing of these episodes or guarantee that patients will correctly recognize the episode, self-administer etripamil and use the cardiac monitor as directed. We also cannot predict with certainty the number or timing of any SVT episodes for those patients that enroll in the trial. Conducting a Phase 3 clinical trial for a PSVT treatment in an at-home setting is paradigm changing, and subject to a number of risks. There is limited, if any, meaningful precedent from which to inform our trial design and make assumptions about patient enrollment and compliance. Accordingly, our Phase 3 trial design is subject to significantly more risks than if there were numerous studies upon which we could model our protocols. Our efficacy and safety databases could take significantly longer to populate than projected, which would add cost to our development program and delay any potential approval of etripamil.

Furthermore, our efforts to build relationships with patient communities may not succeed, which could result in delays in patient enrollment in our clinical trials. In addition, any negative results we may report in clinical trials of etripamil and any future product candidate may make it difficult or impossible to recruit and retain patients in other clinical trials of that same product candidate. For example, we reported a failed primary endpoint from our NODE-301 trial in March 2020. Delays or failures in planned patient enrollment or retention may result in increased costs, program delays or both, which could have a harmful effect on our ability to develop etripamil or any future product candidates or could render further development impossible. In addition, we expect to rely on CROs and clinical trial sites to ensure proper and timely conduct of our future clinical trials and, while we intend to enter into agreements governing their services, we will be limited in our ability to compel their actual performance. Similarly, our formulation of etripamil is designed to be self-administered as a nasal spray during an SVT episode by patients enrolled in our Phase 3 trials, or during a AFib-RVR episode by patients in our Phase 2 trial. While we expect enrolled patients to adhere to the protocol, our ability to ensure patient compliance is limited.

Our product candidates may cause undesirable side effects or have other properties that could delay or prevent their regulatory approval, limit the commercial potential or result in significant negative consequences following any potential marketing approval.

During the conduct of clinical trials, patients report changes in their health, including illnesses, injuries and discomforts, to their doctor. Often, it is not possible to determine whether or not the product candidate being studied caused these conditions. Regulatory authorities may draw different conclusions or require additional testing to confirm these determinations, if they occur. For example, in our Phase 2 clinical trial for PSVT, three serious adverse events, or SAEs, were considered possibly related to etripamil, including a second degree AV block that subsequently resolved. Calcium channel blockers have known side effects, such as slowing the heart rate below normal levels and hypotension, or low blood pressure. While we designed etripamil to have a short pharmacodynamic effect to lower these risks, if etripamil is not quickly metabolized as designed, these known side effects may become more pronounced in patients who use etripamil.

In addition, it is possible that as we test etripamil or any future product candidates in larger, longer and more extensive clinical trials, such as our Phase 3 clinical trials, or as use of etripamil or any future 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 or patients. Many times, side effects are only detectable after investigational drugs are tested in large-scale pivotal trials or, in some cases, after they are made available to patients on a commercial scale after approval. If additional clinical experience indicates that etripamil or any future product candidates have side effects or causes serious or life-threatening side effects, the development of the product candidate may fail or be delayed, or, if the product candidate has received regulatory approval, such approval may be revoked, which would harm our business, prospects, operating results and financial condition.

Interim, "top-line" 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 publish interim, "top-line" or preliminary data from our clinical trials. 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. Preliminary or "top-line" 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, interim and preliminary data should be viewed with caution until the final data are available. Differences between preliminary or interim data and final data could significantly harm our business prospects and may cause the trading price of our common shares to fluctuate significantly.

As an organization, we have never successfully completed pivotal clinical trials, and we may be unable to do so for any product candidates we may develop, including our pivotal Phase 3 clinical trials for the treatment of PSVT.

We will need to successfully complete pivotal clinical trials in order to obtain the approval of the FDA and other regulatory agencies to market etripamil or any of our other product candidates. Carrying out later-stage clinical trials and the submission of a successful NDA is a complicated process. As an organization, we have only completed one Phase 3 clinical trial, we have other trials ongoing, and we have limited experience in preparing, submitting and prosecuting regulatory filings. Due to our limited experience with later stage trials, we may be unable to successfully and efficiently execute and complete necessary clinical trials in a way that leads to NDA submission and approval of etripamil for the treatment of PSVT. We may require more time and incur greater costs than our competitors and may not succeed in obtaining regulatory approvals of product candidates that we develop. Failure to commence or complete, or delays in, our planned clinical trials could prevent us from or delay us in commercializing etripamil for the treatment of PSVT.

We may explore strategic collaborations that may never materialize, or we may be required to relinquish important rights to and control over the development of our product candidates to any future collaborators.

We intend to periodically explore a variety of possible strategic collaborations in an effort to gain access to additional product candidates or resources. At the current time, we cannot predict what form such a strategic collaboration might take. We are likely to face significant competition in seeking appropriate strategic collaborators, and strategic collaborations can be complicated and time consuming to negotiate and document. We may not be able to negotiate strategic collaborations on acceptable terms, or at all. We are unable to predict when, if ever, we will enter into any strategic collaborations because of the numerous risks and uncertainties associated with establishing them.

Future collaborations could subject us to a number of risks, including:

- we may be required to undertake the expenditure of substantial operational, financial and management resources;
- we may be required to issue equity securities that would dilute our shareholders' percentage ownership of our company;

- we may be required to assume substantial actual or contingent liabilities;
- we may not be able to control the amount and timing of resources that our strategic collaborators devote to the development or commercialization of our product candidates;
- strategic collaborators may select indications or design clinical trials in a way that may be less successful than if we were doing so;
- strategic collaborators may delay clinical trials, provide insufficient funding, terminate a clinical trial or abandon a product candidate, repeat or conduct new clinical trials or require a new version of a product candidate for clinical testing;
- strategic collaborators may not pursue further development of products resulting from the strategic collaboration arrangement or may elect to discontinue research and development programs;
- strategic collaborators may not commit adequate resources to the marketing and distribution of our product candidates, limiting our potential revenues from these products;
- disputes may arise between us and our strategic collaborators that result in the delay or termination of the research or development of our product candidates or that result in costly litigation or arbitration that diverts management's attention and consumes resources;
- strategic collaborators may experience financial difficulties;
- strategic collaborators may not properly maintain or defend our intellectual property rights or may use our proprietary information in a manner that could jeopardize or invalidate our proprietary information or expose us to potential litigation;
- business combinations or significant changes in a strategic collaborator's business strategy may adversely affect a strategic collaborator's willingness or ability to complete its obligations under any arrangement;
- strategic collaborators could decide to move forward with a competing product candidate developed either independently or in collaboration with others, including our competitors; and
- strategic collaborators could terminate the arrangement or allow it to expire, which would delay the development and may increase the cost of developing our product candidates.

Risks Related to the Commercialization of Our Product Candidates

If we are unable to establish sales and marketing capabilities or enter into agreements with third parties to market and sell etripamil or any future product candidates, we may not be successful in commercializing etripamil or any future product candidates, if and when they are approved.

To successfully commercialize etripamil or any future product candidate that may result from our development programs, we will need to build out our sales and marketing capabilities, either on our own or with others. The establishment and development of our own commercial team or the establishment of a contract field force to market any product candidate we may develop will be expensive and time consuming and could delay any drug launch. Moreover, we cannot be certain that we will be able to successfully develop this capability. We may seek to enter into collaborations with other entities to use their established marketing and distribution capabilities, but we may be unable to enter into such agreements on favorable terms, if at all. If any current or future collaborators do not commit sufficient resources to commercialize our product candidates, or we are unable to develop the necessary capabilities on our own, we may be unable to generate sufficient revenue to sustain our business. We may compete with many companies that currently have extensive, experienced, and well-funded marketing and sales operations to recruit, hire, train and retain

marketing and sales personnel. We will likely also face competition if we seek third parties to assist us with the sales and marketing efforts of etripamil and any future product candidates. Without an internal team or the support of a third party to perform marketing and sales functions, we may be unable to compete successfully against these more established companies.

Even if etripamil or any future product candidates receive marketing approval, they may fail to achieve market acceptance by physicians, patients, third-party payors or others in the medical community necessary for commercial success.

Even if etripamil or any future product candidates receive marketing approval, they may fail to gain market acceptance by physicians, patients, third-party payors and others in the medical community. If such product candidates do not achieve an adequate level of acceptance, we may not generate significant drug revenue and may not become profitable. The degree of market acceptance of etripamil or any future product candidates, if approved for commercial sale, will depend on a number of factors, including but not limited to:

- the convenience and ease of administration compared to alternative treatments and therapies;
- the willingness of the target patient population to try new therapies and of physicians to prescribe these therapies;
- the efficacy and potential advantages compared to alternative treatments and therapies;
- the effectiveness of sales and marketing efforts;
- the prevalence and severity of any side effects;
- the strength of our relationships with patient communities;
- the cost of treatment in relation to alternative treatments and therapies, including any similar generic treatments;
- our ability to offer such drug for sale at competitive prices;
- the strength of marketing and distribution support;
- the availability of third-party coverage and adequate reimbursement; any restrictions on the use of the drug together with other medications; and the awareness and support from key opinion leaders in cardiology.

Our efforts to educate physicians, patients, third-party payors and others in the medical community on the benefits of etripamil or any future product candidates may require significant resources and may never be successful. Such efforts may require more resources than are typically required due to the potential of etripamil to shift the treatment paradigm away from acute-care settings to self-administration. Because we expect sales of etripamil or any future product candidates, if approved, to generate substantially all of our revenues for the foreseeable future, the failure of these product candidates to find market acceptance would harm our business.

Even if we successfully obtain approval for etripamil, its success will be dependent on its proper use.

While we have designed etripamil to be self-administered, we cannot control the successful use of the product. While we have conducted, and intend in the future to conduct, human factors studies to determine how to optimize the instructions for use, the results in our clinical trials may not be replicated by users in the future. If we are not successful in promoting the proper use of etripamil, if approved, we may not be able to achieve market acceptance or effectively commercialize the drug. In addition, even in the event of proper use of etripamil, individual devices may fail. Increasing the scale of production inherently creates increased risk of manufacturing errors, and we may not be able to adequately inspect every

device that is produced, and it is possible that individual devices may fail to perform as designed. Manufacturing errors could negatively impact market acceptance of any of our product candidates that receive approval, result in negative press coverage, or increase our liability.

If the market opportunities for etripamil and any future product candidates are smaller than we estimate, our business may suffer.

Our eligible patient population may differ significantly from the actual market addressable by our product candidates. Our projections of both the number of people who have these conditions, as well as the subset of people with these diseases who have the potential to benefit from treatment with our product candidates, are based on our beliefs and estimates. These estimates have been derived from a variety of sources, including the scientific literature, insurance claims databases or market research, and may prove to be incorrect. Further, new studies may change the estimated incidence or prevalence of these diseases. The number of patients may turn out to be lower than expected. Likewise, the potentially addressable patient population for each of our product candidates may be limited or may not be amenable to treatment with our product candidates, and new patients may become increasingly difficult to identify or access. If the market opportunities for our product candidates are smaller than we estimate, our business and results of operations could be adversely affected.

We may face substantial competition, which may result in others developing or commercializing drugs before or more successfully than us.

The development and commercialization of new drugs is highly competitive. We may face competition from major pharmaceutical companies, specialty pharmaceutical companies and biotechnology companies worldwide. Potential competitors also include academic institutions, government agencies and other public and private research organizations that conduct research, seek patent protection and establish collaborative arrangements for research, development, manufacturing and commercialization.

More established companies may have a competitive advantage over us due to their greater size, resources and institutional experience. In particular, these companies have greater experience and expertise in securing reimbursement, government contracts and relationships with key opinion leaders, conducting testing and clinical trials, obtaining and maintaining regulatory approvals and distribution relationships to market products and marketing approved drugs. These companies also have significantly greater research and marketing capabilities than we do. If we are not able to compete effectively against existing and potential competitors, our business and financial condition may be harmed.

As a result of these factors, our competitors may obtain regulatory approval of their drugs before we are able to, which may limit our ability to develop or commercialize etripamil and any future product candidates. Our competitors may also develop therapies that are safer, more effective, more widely accepted or less expensive than ours, and may also be more successful than we in manufacturing and marketing their drugs. These advantages could render our product candidates obsolete or non-competitive before we can recover the costs of such product candidates' development and commercialization.

Mergers and acquisitions in the pharmaceutical and biotechnology industries may result in even more resources being concentrated among a smaller number of our competitors. Smaller and early stage companies may also prove to be significant competitors, particularly through collaborative arrangements with large and established companies. These third parties compete with us in recruiting and retaining qualified scientific, management and commercial personnel, establishing clinical trial sites and subject registration for clinical trials, as well as in acquiring technologies complementary to, or necessary for, our programs.

If we commercialize etripamil or any future product candidates outside of the United States, a variety of risks associated with international operations could harm our business.

We intend to seek approval to market etripamil outside of the United States, and may do so for future product candidates. If we market approved products outside of the United States, we expect that we will be subject to additional risks in commercialization including:

- different regulatory requirements for approval of therapies in foreign countries;
- reduced protection for intellectual property rights;
- unexpected changes in tariffs, trade barriers and regulatory requirements;
- economic weakness, including inflation, or political instability in particular foreign economies and markets;
- compliance with tax, employment, immigration and labor laws for employees living or traveling abroad;
- foreign currency fluctuations, which could result in increased operating expenses and reduced revenues, and other obligations incident to doing business in another country;
- foreign reimbursement, pricing and insurance regimes;
- workforce uncertainty in countries where labor unrest is more common than in the United States;
- production shortages resulting from any events affecting raw material supply or manufacturing capabilities abroad; and
- business interruptions resulting from pandemics and public health emergencies, including those related to COVID-19 coronavirus, geopolitical actions, including war and terrorism or natural disasters including earthquakes, typhoons, floods and fires.

We have no prior experience in these areas. In addition, there are complex regulatory, tax, labor and other legal requirements imposed by many of the individual countries in and outside of Europe with which we will need to comply. Many biopharmaceutical companies have found the process of marketing their own products in foreign countries to be very challenging.

Coverage and adequate reimbursement may not be available for etripamil or any future product candidates, which could make it difficult for us to gain market acceptance.

Market acceptance and sales of any product candidates that we commercialize, if approved, will depend in part on the extent to which reimbursement for these drugs and related treatments will be available from third-party payors, including government health administration authorities, managed care organizations and other private health insurers. Third-party payors decide for which therapies and establish reimbursement levels. While no uniform policy for coverage and reimbursement exists in the United States, third-party payors often rely upon Medicare coverage policy and payment limitations in setting their own coverage and reimbursement policies. However, decisions regarding the extent of coverage and amount of reimbursement to be provided for any product candidates that we develop will be made on a payor-by-payor basis. Therefore, one payor's determination to provide coverage for a drug does not assure that other payors will also provide coverage, and adequate reimbursement, for the drug. Additionally, a third-party payor's decision to provide coverage for a therapy does not imply that an adequate reimbursement rate will be approved. Each payor determines whether or not it will provide coverage for a therapy, what amount it will pay the manufacturer for the therapy, and on what tier of its formulary it will be placed. The position on a payor's list of covered drugs, or formulary, generally determines the co-payment that a patient will need to make to obtain the therapy and can strongly influence the

adoption of such therapy by patients and physicians. Patients who are prescribed treatments for their conditions and providers prescribing such services generally rely on third-party payors to reimburse all or part of the associated healthcare costs. Patients are unlikely to use our products unless coverage is provided and reimbursement is adequate to cover a significant portion of the cost of our products.

Third-party payors have attempted to control costs by limiting coverage and the amount of reimbursement for particular medications. We cannot be sure that coverage and reimbursement will be available for any drug that we commercialize and, if reimbursement is available, what the level of reimbursement will be. Inadequate coverage and reimbursement may impact the demand for, or the price of, any drug for which we obtain marketing approval. If coverage and adequate reimbursement are not available, or are available only to limited levels, we may not be able to successfully commercialize etripamil or any future product candidates that we develop.

In addition, we expect that the increased emphasis on managed care and cost containment measures in the United States by third-party payors and government authorities to continue and will place pressure on pharmaceutical pricing and coverage. Coverage policies and third-party reimbursement rates may change at any time. Therefore, even if favorable coverage and reimbursement status is attained for one or more drug products for which we receive regulatory approval, less favorable coverage policies and reimbursement rates may be implemented in the future. If we are unable to obtain and maintain sufficient third-party coverage and adequate reimbursement for our drug products, the commercial success of our drug products may be greatly hindered and our financial condition and results of operations may be materially and adversely affected.

Product liability lawsuits against us could cause us to incur substantial liabilities and could limit commercialization of any product candidates that we may develop.

We face an inherent risk of product liability exposure related to the testing of etripamil or any future product candidates in clinical trials and may face an even greater risk if we commercialize any product candidate that we may develop. If we cannot successfully defend ourselves against claims that any such product candidates caused injuries, we could incur substantial liabilities. Regardless of merit or eventual outcome, liability claims may result in:

- decreased demand for any product candidate that we may develop;
- loss of revenue;
- substantial monetary awards to trial participants or patients;
- significant time and costs to defend the related litigation;
- withdrawal of clinical trial participants;
- increased insurance costs;
- the inability to commercialize any product candidate that we may develop; and injury to our reputation and significant negative media attention.

Although we maintain clinical trial liability insurance coverage with maximum coverage of $10 million per incident and an aggregate loss limit of $10 million such insurance may not be adequate to cover all liabilities that we may incur with a medical product during the clinical trials. We anticipate that we will need to increase our insurance coverage each time we commence a clinical trial and maintain a product liability insurance if we successfully commercialize any product candidate. Insurance coverage is increasingly expensive. We may not be able to maintain insurance coverage at a reasonable cost or in an amount adequate to satisfy any liability that may arise.

Risks Related to Regulatory Compliance

Even if we obtain and maintain approval for etripamil or any future product candidates from the FDA, we may never obtain approval of etripamil or any future product candidates outside of the United States, which would limit our market opportunities and could harm our business.

Approval of a product candidate in the United States by the FDA does not ensure approval of such product candidate by regulatory authorities in other countries or jurisdictions, and approval by one foreign regulatory authority does not ensure approval by regulatory authorities in other foreign countries or by the FDA. Sales of etripamil or any future product candidates outside of the United States will be subject to foreign regulatory requirements governing clinical trials and marketing approval. Even if the FDA grants marketing approval for a product candidate, comparable foreign regulatory authorities also must approve the manufacturing and marketing of the product candidate in those countries. Approval procedures vary among jurisdictions and can involve requirements and administrative review periods different from, and more onerous than, those in the United States, including additional preclinical studies or clinical trials. In many countries outside the United States, a product candidate must be approved for reimbursement before it can be approved for sale in that country. In some cases, the price that we intend to charge for any product candidates, if approved, is also subject to approval. Obtaining approval for etripamil or any future product candidates in the European Union from the European Commission following the opinion of the European Medicines Agency, if we choose to submit a marketing authorization application there, would be a lengthy and expensive process. Even if a product candidate is approved, the FDA or the European Commission, as the case may be, may limit the indications for which the drug may be marketed, require extensive warnings on the drug labeling or require expensive and time-consuming additional clinical trials or reporting as conditions of approval. Obtaining foreign regulatory approvals and compliance with foreign regulatory requirements could result in significant delays, difficulties and costs for us and could delay or prevent the introduction of etripamil or any future product candidates in certain countries.

Further, clinical trials conducted in one country may not be accepted by regulatory authorities in other countries. Also, regulatory approval for our product candidates may be withdrawn. If we fail to comply with the regulatory requirements, our target market will be reduced and our ability to realize the full market potential of etripamil or any future product candidates will be harmed and our business, financial condition, results of operations and prospects could be harmed.

Even if we obtain regulatory approval for etripamil or any future product candidates, they will remain subject to ongoing regulatory oversight.

Even if we obtain regulatory approvals for etripamil or any future product candidates, such approvals will be subject to ongoing regulatory requirements for manufacturing, labeling, packaging, storage, advertising, promotion, sampling, record-keeping and submission of safety and other post-market information. Any regulatory approvals that we receive for etripamil or any future product candidates may also be subject to a REMS, limitations on the approved indicated uses for which the drug may be marketed or to the conditions of approval, or contain requirements for potentially costly post-marketing testing, including Phase 4 trials, and surveillance to monitor the quality, safety and efficacy of the drug. Such regulatory requirements may differ from country to country depending on where we have received regulatory approval.

In addition, drug manufacturers and their facilities are subject to payment of user fees and continual review and periodic inspections by the FDA and other regulatory authorities for compliance with cGMP requirements and adherence to commitments made in the NDA or foreign marketing application. If we, or a regulatory authority, discover previously unknown problems with a drug, such as adverse events of unanticipated severity or frequency, or problems with the facility where the drug is manufactured or if a regulatory authority disagrees with the promotion, marketing or labeling of that drug, a regulatory authority may impose restrictions relative to that drug, the manufacturing facility or us, including requesting a recall or requiring withdrawal of the drug from the market or suspension of manufacturing.

If we fail to comply with applicable regulatory requirements following approval of etripamil or any future product candidates, a regulatory authority may:

- issue an untitled letter or warning letter asserting that we are in violation of the law;
- seek an injunction or impose administrative, civil or criminal penalties or monetary fines;
- suspend or withdraw regulatory approval;
- suspend any ongoing clinical trials;
- refuse to approve a pending NDA or comparable foreign marketing application or any supplements thereto submitted by us or our partners;
- restrict the marketing or manufacturing of the drug;
- seize or detain the drug or otherwise require the withdrawal of the drug from the market;
- refuse to permit the import or export of product candidates; or
- refuse to allow us to enter into supply contracts, including government contracts.

Moreover, 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. Physicians, on the other hand, may prescribe products for off-label uses. Although the FDA and other regulatory agencies do not regulate a physician's choice of drug treatment made in the physician's independent medical judgment, they do restrict promotional communications from companies or their sales force with respect to off-label uses of products for which marketing clearance has not been issued. However, biopharmaceutical companies may share truthful and not misleading information that is otherwise consistent with the labeling. The FDA and other agencies actively enforce the laws and regulations prohibiting the promotion of off-label uses, and a company that is found to have improperly promoted off-label uses may be subject to significant civil, criminal and administrative penalties.

Any government investigation of alleged violations of law could require us to expend significant time and resources in response and could generate negative publicity. The occurrence of any event or penalty described above may inhibit our ability to commercialize etripamil or any future product candidates and harm our business, financial condition, results of operations and prospects.

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, which would adversely affect our business, prospects, financial condition and results of operations.

In addition, we cannot predict the likelihood, nature or extent of government regulation that may arise from future legislation or administrative or executive action, either in the United States or abroad. Namely, the Trump administration took several executive actions, including the issuance of a number of Executive Orders, that could impose significant burdens on, or otherwise materially delay, the FDA's ability to engage in routine regulatory and oversight activities such as implementing statutes through rulemaking, issuance of guidance, and review and approval of marketing applications. It is difficult to predict how these executive actions, including the Executive Orders, will be implemented and the extent to which they will affect the FDA's ability to exercise its regulatory authority. If these executive actions impose constraints on the FDA's ability to engage in oversight and implementation activities in the normal course, our business may be negatively impacted.

Our relationships with customers, physicians, and third-party payors are subject, directly or indirectly, to federal and state healthcare fraud and abuse laws, false claims laws, health information privacy and security laws, and other healthcare laws and regulations. If we are unable to comply, or have not fully complied, with such laws, we could face substantial penalties.

Healthcare providers, including physicians and third-party payors in the United States and elsewhere will play a primary role in the recommendation and prescription of any product candidates for which we obtain marketing approval. Our current and future arrangements with healthcare professionals, principal investigators, consultants, customers and third-party payors subject us to various federal and state fraud and abuse laws, data privacy and security laws, transparency laws and other healthcare laws that may constrain the business or financial arrangements and relationships through which we research, sell, market, and distribute our products, if we obtain marketing approval.

The federal Anti-Kickback Statute prohibits the offer, receipt, or payment of remuneration in exchange for or to induce the referral of patients or the use of products or services that would be paid for in whole or part by Medicare, Medicaid or other federal healthcare programs. Remuneration has been broadly defined to include anything of value, including cash, improper discounts, and free or reduced price items and services. Additionally, the intent standard under the federal Anti-Kickback Statute was amended by the Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act of 2010, or collectively, PPACA, to a stricter standard such that a person or entity does not need to have actual knowledge of the statute or specific intent to violate it in order to have committed a violation. Further, PPACA codified case law that a claim including items or services resulting from a violation of the federal Anti-Kickback Statute constitutes a false or fraudulent claim for purposes of the False Claims Act.

The federal false claims, including the False Claims Act, and civil monetary penalties laws, which prohibit individuals or entities from, among other things, knowingly presenting, or causing to be presented, false or fraudulent claims for payment of federal funds, and knowingly making, or causing to be made, a false record or statement material to a false or fraudulent claim to avoid, decrease or conceal an obligation to pay money to the federal government.

The federal Health Information Insurance Portability and Accountability Act of 1996, or HIPAA, prohibits, among other things, knowingly and willfully executing, or attempting to execute, a scheme to defraud any healthcare benefit program, or knowingly and willfully falsifying, concealing or covering up a material fact or making any materially false statement, in connection with the delivery of, or payment for, healthcare benefits, items or services. Similar to the U.S. federal Anti-Kickback Statute, a person or entity does not need to have actual knowledge of the statute or specific intent to violate it in order to have committed a violation.

HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act of 2009, or HITECH, also imposes, among other things, certain standards and obligations on covered entities including certain healthcare providers, health plans and healthcare clearinghouses, and their respective business associates that create, receive, maintain, or transmit individually identifiable health information for or on behalf of a covered entity as well as their covered subcontractors relating to the privacy, security, transmission and breach reporting of individually identifiable health information.

The federal Physician Payments Sunshine Act, and its implementing regulations, require certain manufacturers of drugs, devices, biologics and medical supplies that are reimbursable under Medicare, Medicaid, or the Children’s Health Insurance Program to report annually to Centers for Medicare & Medicaid Services information related to certain payments and other transfers of value to physicians (defined to include doctors, dentists, optometrists, podiatrists and chiropractors), and teaching hospitals, as well as ownership and investment interests held by the physicians described above and their immediate family members. Beginning in 2022, applicable manufacturers also will be required to report such information regarding its relationships with physician assistants, nurse practitioners, clinical nurse specialists, anesthesiologist assistants, certified registered nurse anesthetists and certified nurse midwives during the previous year.

We will also be subject to healthcare regulation and enforcement by the U.S. federal government and the states and any other countries in which we conduct our business, including our research, and the sales, marketing and distribution of our product candidates and products once they have obtained marketing authorization.

Analogous state and foreign anti-kickback and false claims laws that may apply to sales or marketing arrangements and claims involving healthcare items or services reimbursed by non-governmental third party payors, including private insurers, or that apply regardless of payor; state laws that require pharmaceutical companies to comply with the pharmaceutical industry's voluntary compliance guidelines and the relevant compliance guidance promulgated by the federal government; state and local laws that require drug manufacturers to report information related to payments and other transfers of value to physicians and other healthcare providers or marketing expenditures; state laws that require the reporting of information related to drug pricing; state and local laws requiring the registration of pharmaceutical sales representatives; and state and foreign laws governing the privacy and security of health information in some circumstances, many of which differ from each other in significant ways and often are not preempted by HIPAA, thus complicating compliance efforts.

Ensuring that our business arrangements with third parties comply with applicable healthcare laws and regulations will likely be costly. It is possible that governmental authorities will conclude that our business practices may not comply with current or future statutes, regulations or case law involving applicable fraud and abuse or other healthcare laws and regulations. If our operations are found to be in violation of any of these laws or any other governmental regulations that may apply to us, we may be subject to significant civil, criminal and administrative penalties, damages, fines, disgorgement, imprisonment, exclusion from participating in government funded healthcare programs, such as Medicare and Medicaid, 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, contractual damages, reputational harm and the curtailment or restructuring of our operations.

If the physicians or other providers or entities with whom we expect to do business are found not to be in compliance with applicable laws, they may be subject to significant criminal, civil or administrative sanctions, including exclusions from government funded healthcare programs. Even if resolved in our favor, litigation or other legal proceedings relating to healthcare laws and regulations may cause us to incur significant expenses and could distract our technical and management personnel from their normal responsibilities. In addition, there could be public announcements of the results of hearings, motions or other interim proceedings or developments. If securities analysts or investors perceive these results to be negative, it could have a substantial adverse effect on the price of our common shares. Such litigation or proceedings could substantially increase our operating losses and reduce the resources available for development, manufacturing, sales, marketing or distribution activities. Uncertainties resulting from the initiation and continuation of litigation or other proceedings relating to applicable healthcare laws and regulations could have a material adverse effect on our ability to compete in the marketplace.

Healthcare legislative reform measures may have a negative impact on our business and results of operations.

In the United States and some foreign jurisdictions, there have been, and continue to be, several legislative and regulatory changes and proposed changes regarding the healthcare system that could prevent or delay marketing approval of product candidates, restrict or regulate post-approval activities, and affect our ability to profitably sell any product candidates for which we obtain marketing approval. In particular, there have been and continue to be a number of initiatives at the U.S. federal and state levels that seek to reduce healthcare costs and improve the quality of healthcare. For example, in March 2010 the PPACA, was passed, which substantially changed the way healthcare is financed by both governmental and private payors in the United States. There have been executive, judicial and Congressional challenges to certain aspects of the PPACA.. For example, the Tax Cuts and Jobs Act of 2017, or the Tax Act, was enacted, which included a provision that repealed, effective January 1, 2019, the tax-based shared responsibility payment imposed by the PPACA on certain individuals who fail to maintain qualifying health coverage for all or part of a year that is commonly referred to as the "individual mandate." In addition, the 2020 federal spending package permanently eliminated, effective January 1, 2020, the PPACA-mandated "Cadillac" tax on high-cost employer-sponsored health coverage and medical device tax and, effective January 1, 2021, also eliminated the health insurer tax. Additionally, on December 14, 2018, a Texas U.S. District Court Judge ruled that the PPACA is unconstitutional in its entirety because the "individual mandate" was repealed by Congress as part of the Tax Act. Additionally, on December 18, 2019, the U.S. Court of Appeals for the 5th Circuit upheld the District Court ruling that the individual mandate was unconstitutional and remanded the case back to the District Court to determine whether the remaining provisions of the PPACA are invalid as well. The United States Supreme Court is currently reviewing this case. It is unclear how such litigation and other efforts to repeal and replace the PPACA will impact the PPACA and our

business. Although the U.S. Supreme Court has not yet ruled on the constitutionality of the PPACA, on January 28, 2021, President Biden issued an executive order to initiate a special enrollment period from February 15, 2021 through May 15, 2021 for purposes of obtaining health insurance coverage through the PPACA marketplace. The executive order also instructs certain governmental agencies to review and reconsider their existing policies and rules that limit access to healthcare, including among others, reexamining Medicaid demonstration projects and waiver programs that include work requirements, and policies that create unnecessary barriers to obtaining access to health insurance coverage through Medicaid or the PPACA. It is unclear how the Supreme Court ruling, other such litigation, and the healthcare reform measures of the Biden administration will impact the PPACA and our business.

Further, in the United States there has been heightened governmental scrutiny over the manner in which manufacturers set prices for their marketed products, which has resulted in several Congressional inquiries and proposed and enacted federal and state legislation designed to, among other things, bring more transparency to drug pricing, reduce the cost of prescription drugs under government payor programs, and review the relationship between pricing and manufacturer patient programs. At the federal level, the Trump administration used several means to propose or implement drug pricing reform, including through federal budget proposals, executive orders and policy initiatives. For example, on July 24, 2020 and September 13, 2020, the Trump administration announced several executive orders related to prescription drug pricing that attempted to implement several of the administration's proposals.The FDA also released a final rule on September 24, 2020, effective November 30, 2020, implementing a portion of the importation executive order providing guidance for states to build and submit importation plans for drugs from Canada. Further, on November 20, 2020, HHS finalized a regulation removing safe harbor protection for price reductions from pharmaceutical manufacturers to plan sponsors under Part D, either directly or through pharmacy benefit managers, unless the price reduction is required by law. The implementation of the rule has been delayed by the Biden administration from January 1, 2022 to January 1, 2023 in response to ongoing litigation. The rule also creates a new safe harbor for price reductions reflected at the point-of-sale, as well as a new safe harbor for certain fixed fee arrangements between pharmacy benefit managers and manufacturers, the implementation of which have also been delayed pending review by the Biden administration until March 22, 2021. On November 20, 2020, CMS issued an interim final rule implementing the Trump Administration's Most Favored Nation executive order, which would tie Medicare Part B payments for certain physician-administered drugs to the lowest price paid in other economically advanced countries, effective January 1, 2021. On December 28, 2020, the United States District Court in Northern California issued a nationwide preliminary injunction against implementation of the interim final rule. It is unclear whether the Biden administration will work to reverse these measures or pursue similar policy initiatives. At the state level, legislatures have increasingly passed legislation and implemented regulations designed to control pharmaceutical and biological 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 U.S. healthcare reform measures will be adopted in the future, any of which could limit the amounts that the U.S. federal government will pay for healthcare products and services, which could result in reduced demand for etripamil or any future product candidates or additional pricing pressures. It is also possible that additional governmental action will be taken in response to the COVID-19 pandemic.

In addition, other legislative changes have been proposed and adopted since the PPACA was enacted. On August 2, 2011, the Budget Control Act of 2011 was signed into law, which includes reductions to Medicare payments to providers of 2% per fiscal year, which went into effect on April 1, 2013 and, due to subsequent legislative amendments to the statute, will remain in effect through 2030 with the exception of a temporary suspension from May 1, 2020 through March 31, 2021 due to the COVID-19 pandemic, unless additional Congressional action is taken. On January 2, 2013, the American Taxpayer Relief Act of 2012 was signed into law, which, among other things, reduced Medicare payments to several providers, including hospitals, and increased the statute of limitations period for the government to recover overpayments to providers from three to five years.

We cannot predict the likelihood, nature or extent of health reform initiatives that may arise from future legislation or administrative action in the United States, particularly in light of the new presidential administration, or any other jurisdiction. If we or any third parties we may engage are slow or unable to adapt to changes in existing or new requirements or policies, or if the we or such third parties are not able to maintain regulatory compliance, etripamil or any future product candidates we may develop may lose any regulatory approval that may have been obtained and we may not achieve or sustain profitability.

Our business involves the use of hazardous materials and we and our third-party manufacturers and suppliers must comply with environmental laws and regulations, which can be expensive and restrict how we do business.

Our research and development activities and our third-party manufacturers' and suppliers' activities involve the controlled storage, use and disposal of hazardous materials owned by us, including the components of etripamil and any future product candidates and other hazardous compounds. We and our manufacturers and suppliers are subject to laws and regulations governing the use, manufacture, storage, handling and disposal of these hazardous materials. In some cases, these hazardous materials and various wastes resulting from their use are stored at our and our manufacturers' facilities pending their use and disposal. We cannot eliminate the risk of contamination, which could cause an interruption of our commercialization efforts, research and development efforts and business operations, environmental damage resulting in costly clean-up and liabilities under applicable laws and regulations governing the use, storage, handling and disposal of these materials and specified waste products. Although we believe that the safety procedures utilized by our third-party manufacturers for handling and disposing of these materials generally comply with the standards prescribed by these laws and regulations, we cannot guarantee that this is the case or eliminate the risk of accidental contamination or injury from these materials. In such an event, we may be held liable for any resulting damages and such liability could exceed our resources and state or federal or other applicable authorities may curtail our use of certain materials and/or interrupt our business operations. Furthermore, environmental laws and regulations are complex, change frequently and have tended to become more stringent. We cannot predict the impact of such changes and cannot be certain of our future compliance. We do not currently carry hazardous waste insurance coverage.

Risks Related to Our Dependence on Third Parties

We will rely on third parties to produce clinical and commercial supplies of etripamil and any future product candidates.

We do not own or operate facilities for drug manufacturing, storage and distribution, or testing. We are dependent on third parties to manufacture the clinical supplies of etripamil and any future product candidates. The facilities used by our contract manufacturers to manufacture etripamil and any future product candidates must be approved by the FDA pursuant to inspections that will be conducted after we submit our NDA to the FDA. We do not control the manufacturing process of, and are completely dependent on, our contract manufacturing partners for compliance with the regulatory requirements, known as cGMPs for manufacture of active drug substances, nasal spray device, and finished product candidates. If our contract manufacturers cannot successfully manufacture material that conforms to our specifications and the strict regulatory requirements of the FDA or others, we will not be able to secure and/or maintain regulatory approval for our product candidates. In addition, we have no control over the ability of our contract manufacturers to maintain adequate quality control, quality assurance and qualified personnel. We intend to use multiple contract manufacturers for clinical and commercial supply of our drug product and drug substance. As such, we will need to demonstrate to the FDA that the drug product and drug substance from these contract manufacturers are comparable, which may include conducting additional equivalence studies. 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. Any significant delay in the supply of a product candidate, or the raw material components thereof, for an ongoing clinical trial due to the need to replace a third-party manufacturer could considerably delay completion of our clinical trials, product testing and potential regulatory approval of our product candidates.

Further, we also will rely on third-party manufacturers to supply us with sufficient quantities of etripamil and any future product candidates, if approved, for commercialization. We do not yet have a commercial supply agreement for commercial quantities of drug substance, drug product or nasal spray device. If we are not able to meet market demand for any approved product, it would negatively affect our ability to generate revenue, harm our reputation, and could have a material and adverse effect on our business and financial condition. Increasing the scale of production inherently creates increased risk of manufacturing errors, and we may not be able to adequately inspect every device that is produced, and it is possible that individual devices may fail to perform as designed. Manufacturing errors could negatively impact market acceptance of any of our product candidates that receive approval, result in negative press coverage, or increase our liability.

Further, our reliance on third-party manufacturers entails risks to which we would not be subject if we manufactured product candidates ourselves, including:

- inability to meet our product specifications and quality requirements consistently;
- delay or inability to procure or expand sufficient manufacturing capacity;
- issues related to scale-up of manufacturing;
- costs and validation of new equipment and facilities required for scale-up;
- our third-party manufacturers may not be able to execute our manufacturing procedures and other logistical support requirements appropriately;
- our third-party manufacturers may fail to comply with cGMP-compliance and other inspections by the FDA or other comparable regulatory authorities;
- our inability to negotiate manufacturing agreements with third parties under commercially reasonable terms, if at all;
- breach, termination or nonrenewal of manufacturing agreements with third parties in a manner or at a time that is costly or damaging to us;
- reliance on a single source for the nasal spray device;
- our third-party manufacturers may not devote sufficient resources to our product candidates;
- we may not own, or may have to share, the intellectual property rights to any improvements made by our third-party manufacturers in the manufacturing process for our product candidates;
- operations of our third-party manufacturers or suppliers could be disrupted by conditions unrelated to our business or operations, including public health emergencies, such as the COVID-19 pandemic, natural disasters, such as earthquakes, fires or floods, the bankruptcy of the manufacturer or supplier, and carrier disruptions or increased costs that are beyond our control.

In addition, if we enter into a strategic collaboration with a third party for the commercialization of etripamil or any future product candidate, we will not be able to control the amount of time or resources that they devote to such efforts. If any strategic collaborator does not commit adequate resources to the marketing and distribution of etripamil or any future product candidate, it could limit our potential revenues.

Any of these events could lead to clinical trial delays, failure to obtain regulatory approval or affect our ability to successfully commercialize etripamil or any future product candidates once approved. Some of these events could be the basis for FDA action, including injunction, request for recall, seizure, or total or partial suspension of production.

We rely on third parties to conduct, supervise and monitor our preclinical studies and clinical trials, and if those third parties perform in an unsatisfactory manner, it may harm our business.

We have engaged CROs to conduct our Phase 3 clinical trials of etripamil for the treatment of PSVT, and our Phase 2 clinical trial of etripamil for the treatment of AFib-RVR, and we expect to engage a CRO for future clinical trials of etripamil and any future product candidates. We do not currently have the ability to independently conduct any clinical trials. We rely on CROs and clinical trial sites to ensure the proper and timely conduct of our preclinical studies and clinical trials, and we expect to have limited influence over their actual performance. We rely upon CROs to monitor and manage data for our clinical programs, as well as the execution of future nonclinical studies. We expect to control only

certain aspects of our CROs' activities. Nevertheless, we will be responsible for ensuring that each of our preclinical studies and clinical trials is conducted in accordance with the applicable protocol, legal, regulatory and scientific standards, and our reliance on the CROs does not relieve us of our regulatory responsibilities.

We and our CROs are required to comply with the good laboratory practices, or GLPs, and GCPs, which are regulations and guidelines enforced by the FDA and comparable foreign regulatory authorities in the form of International Conference on Harmonization guidelines for any of our product candidates that are in preclinical and clinical development. The regulatory authorities enforce GCPs through periodic inspections of trial sponsors, principal investigators and clinical trial sites. Although we rely on CROs to conduct GCP-compliant clinical trials, we remain responsible for ensuring that each of our GLP preclinical studies and clinical trials is conducted in accordance with its investigational plan and protocol and applicable laws and regulations, and our reliance on the CROs does not relieve us of our regulatory responsibilities. If we or our CROs fail to comply with GCPs, 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. Accordingly, if our CROs fail to comply with these regulations or fail to recruit a sufficient number of subjects, we may be required to repeat clinical trials, which would delay the regulatory approval process.

Our reliance on third parties to conduct clinical trials will result in less direct control over the management of data developed through clinical trials than would be the case if we were relying entirely upon our own staff. Any failure by third parties to prevent unauthorized access, use or disclosure of data, including personal information regarding our patients or employees, could harm our reputation, cause us not to comply with federal and/or state breach notification laws and foreign law equivalents and otherwise subject us to liability under laws and regulations that protect the privacy and security of personal information.

Communicating with CROs and other third parties can be challenging, potentially leading to mistakes as well as difficulties in coordinating activities. Such parties may:

- have staffing difficulties;
- fail to comply with contractual obligations;
- experience regulatory compliance issues;
- experience business disruptions from public health emergencies, such as the COVID-19 pandemic, and accompanying shelter in place orders; or
- undergo changes in priorities or become financially distressed.

These factors may materially adversely affect the willingness or ability of third parties to conduct our clinical trials and may subject us to unexpected cost increases that are beyond our control. If our CROs do not successfully carry out their contractual duties or obligations, fail to meet expected deadlines, fail to comply with regulatory requirements, or if the quality or accuracy of the clinical data they obtain is compromised due to the failure to adhere to our clinical protocols or regulatory requirements or for any other reasons, our clinical trials may be extended, delayed or terminated, and we may not be able to obtain regulatory approval for, or successfully commercialize, any product candidate that we develop. As a result, our financial results and the commercial prospects for any product candidate that we develop would be harmed, our costs could increase, and our ability to generate revenue could be delayed. While we will have agreements governing their activities, our CROs will not be our employees, and we will not control whether or not they devote sufficient time and resources to our future clinical and nonclinical programs. These CROs 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 business. We face the risk of potential unauthorized disclosure or misappropriation of our intellectual property by CROs, which may reduce our trade secret protection and allow our potential competitors to access and exploit our proprietary technology.

If our relationship with any of these CROs terminates, we may not be able to enter into arrangements with alternative CROs or do so on commercially reasonable terms. Switching or adding additional CROs involves substantial cost 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 negatively affect our ability to meet our desired clinical development timelines. Though we intend to manage carefully our relationships with our CROs, 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 negative impact on our business, financial condition and prospects.

In addition, principal investigators for our clinical trials may serve as scientific advisors or consultants to us from time to time and receive compensation in connection with such services. Under certain circumstances, we may be required to report some of these relationships to the FDA. The FDA may conclude that a financial relationship between us and a principal investigator has created a conflict of interest or otherwise affected interpretation of the trial. The FDA may therefore question the integrity of the data generated at the applicable clinical trial site and the utility of the clinical trial itself may be jeopardized. This could result in a delay in approval, or rejection, of our marketing applications by the FDA and may ultimately lead to the denial of marketing approval of etripamil and any future product candidates.

Etripamil is intended to be used with a nasal-spray device, which may result in additional regulatory and supply risks.

Etripamil is administered through a nasal-spray device that we obtain from a single source supplier, and that supplier is relying on multiple component suppliers, some of whom are single source suppliers. There are a limited number of device suppliers that address our particular design requirements. While we intend to explore alternative nasal spray devices for the delivery of etripamil that are produced by other suppliers to have backup sources for future commercial needs, we may not identify other nasal device suppliers that meet our requirements, and such alternative devices may not be as effective at the delivery of etripamil as our current supplier's device. We do not currently have a formal supply agreement with our current sole nasal spray device supplier, and obtain such devices as needed. Even if we reach agreement for commercial supply, if we do not have additional nasal spray device suppliers, our sole supplier may be unable to meet our demands. Unpredictability of supply could have a material adverse effect on our commercialization plans for etripamil, if approved, and could have a material adverse effect on our business and financial condition.

Our finished drug product in the intra-nasal delivery system will be regulated as a drug/device combination product. We may experience delays in obtaining regulatory approval of etripamil given the increased complexity of the review process when approval of the product and a delivery device is sought under a single marketing application. In the United States, each component of a combination product is subject to the requirements established by the FDA for that type of component, whether a drug, biologic, or device. The delivery system device would be subject to FDA device requirements regarding design, performance and validation as well as human factors testing, among other things.

Delays in or failure of the studies conducted by us, or failure of our company, our collaborators, if any, or the third-party providers or suppliers to obtain or maintain regulatory approval could result in increased development costs, delays in or failure to obtain regulatory approval, and associated delays in etripamil reaching the market. Further, failure to successfully develop or supply the device, or to gain or maintain its approval, could adversely affect sales of etripamil.

Risks Related to Our Intellectual Property

If we are unable to obtain and maintain patent protection for etripamil or any future product candidates, or if the scope of the patent protection obtained is not sufficiently broad, our competitors could develop and commercialize drugs similar or identical to ours, and our ability to commercialize successfully our product candidates may be impaired.

Our success depends in large part on our ability to obtain and maintain patent protection in the United States and other countries with respect to etripamil and any future product candidates. We seek to protect our proprietary position by filing patent applications in the United States and abroad related to our product candidates. The patent application and prosecution process is expensive and time-consuming. We may not be able to file and prosecute all necessary or desirable patent applications at a reasonable cost or in a timely manner. We may also fail to identify patentable aspects

of our research and development before it is too late to obtain patent protection. Therefore, these and any of our patents and applications may not be prosecuted and enforced in a manner consistent with the best interests of our business. It is possible that defects of form in the preparation or filing of our patents or patent applications may exist, or may arise in the future, such as with respect to proper priority claims, inventorship, claim scope or patent term adjustments. If any future licensors or licensees are not fully cooperative or disagree with us as to the prosecution, maintenance or enforcement of any patent rights, such patent rights could be compromised and we might not be able to prevent third parties from making, using and selling competing products. If there are material defects in the form or preparation of our patents or patent applications, such patents or applications may be invalid and unenforceable. Moreover, our competitors may independently develop equivalent knowledge, methods and know-how. Any of these outcomes could impair our ability to prevent competition from third parties.

The patent position of biotechnology and pharmaceutical companies generally is highly uncertain. Changes in either the patent laws or interpretation of the patent laws in the United States and other countries may diminish the value of our patents or narrow the scope of our patent protection. In addition, the laws of foreign countries may not protect our rights to the same extent as the laws of the United States. No consistent policy regarding the breadth of claims allowed in biotechnology and pharmaceutical patents has emerged to date in the United States or in many foreign jurisdictions. In addition, the determination of patent rights with respect to pharmaceutical compounds and technologies commonly involves complex legal and factual questions, which has in recent years been the subject of much litigation. As a result, the issuance, scope, validity, enforceability and commercial value of our patent rights are highly uncertain. Furthermore, recent changes in patent laws in the United States, including the America Invents Act of 2011, may affect the scope, strength and enforceability of our patent rights or the nature of proceedings that may be brought by us related to our patent rights.

We may not be aware of all third-party intellectual property rights potentially relating to etripamil or any future product candidates. Publications of discoveries in the scientific literature often lag behind the actual discoveries, and patent applications in the United States and other jurisdictions are typically not published until 18 months after filing, or in some cases not at all. For example, U.S. applications filed before November 28, 2000 and certain U.S. applications filed after that date that will not be filed outside the United States remain confidential until a patent issues. Therefore, we cannot be certain that we were the first to make the inventions claimed in our patents or pending patent applications, or that we were the first to file for patent protection of such inventions. Similarly, should we own any patents or patent applications in the future, we may not be certain that we were the first to file for patent protection for the inventions claimed in such patents or patent applications. As a result, the issuance, scope, validity and commercial value of our patent rights cannot be predicted with any certainty. Moreover, we may be subject to a third-party pre-issuance submission of prior art to the U.S. Patent and Trademark Office, or USPTO, or become involved in opposition, derivation, reexamination, inter parties review, post grant review, or interference proceedings, in the United States or elsewhere, challenging our patent rights or the patent rights of others. An adverse determination in any such submission, proceeding or litigation could reduce the scope of, or invalidate, our patent rights, allow third parties to commercialize our technology or product candidates and compete directly with us, without payment to us, or result in our inability to manufacture or commercialize products without infringing third-party patent rights.

Our pending and future patent applications may not result in patents being issued that protect our technology or product candidates, in whole or in part, or which effectively prevent others from commercializing competitive technologies and products. Even if our patent applications issue as patents, they may not issue in a form that will provide us with any meaningful protection against competing products or processes sufficient to achieve our business objectives, prevent competitors from competing with us or otherwise provide us with any competitive advantage. Our competitors may be able to circumvent our owned or licensed patents by developing similar or alternative technologies or products in a non-infringing manner. Our competitors may seek to market generic versions of any approved products by submitting abbreviated new drug applications to the FDA in which they claim that patents owned or licensed by us are invalid, unenforceable and/or not infringed. Alternatively, our competitors may seek approval to market their own products similar to or otherwise competitive with our products. In these circumstances, we may need to defend and/or assert our patents, including by filing lawsuits alleging patent infringement. In any of these types of proceedings, a court or other agency with jurisdiction may find our patents invalid and/or unenforceable.

The issuance of a patent is not conclusive as to its inventorship, scope, validity or enforceability, and our owned and licensed patents may be challenged in the courts or patent offices in the United States and abroad. Such challenges may result in loss of exclusivity or freedom to operate or in patent claims being narrowed, invalidated or held unenforceable, in whole or in part, which could limit our ability to stop others from using or commercializing similar or identical technology and products, or limit the duration of the patent protection of our technology and products. In addition, given the amount of time required for the development, testing and regulatory review of new product candidates, patents protecting such candidates might expire before or shortly after such candidates are commercialized.

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

The USPTO and various foreign governmental 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 fees, renewal fees, annuity fees and various other government fees on patents and/or applications will have to be paid to the USPTO and various government patent agencies outside of the United States over the lifetime of our owned patents and/or applications and any patent rights we may own or license in the future. We rely on our outside counsel to pay these fees due to non-U.S. patent agencies. The USPTO and various non-U.S. government patent agencies require compliance with several procedural, documentary, fee payment and other similar provisions during the patent application process. We employ reputable law firms and other professionals to help us comply.

Non-compliance events that could result in abandonment or lapse of a patent or patent application include, but are not limited to, failure to respond to official actions within prescribed time limits, non-payment of fees and failure to properly legalize and submit formal documents. If we fail to maintain the patents and patent applications covering our products or technologies, we may not be able to stop a competitor from marketing products that are the same as or similar to etripamil or any future product candidates, which would have a material adverse effect on our business. In many cases, an inadvertent lapse can be cured by payment of a late fee or by other means in accordance with the applicable rules. There are situations, however, in which non-compliance can result in abandonment or lapse of the patent or patent application, resulting in partial or complete loss of patent rights in the relevant jurisdiction. In such an event, potential competitors might be able to enter the market and this circumstance could harm our business.

Patent terms may be inadequate to protect our competitive position on our product candidates for an adequate amount of time.

Given the amount of time required for the development, testing and regulatory review of new product candidates, such as etripamil, patents protecting such candidates might expire before or shortly after such candidates are commercialized. We expect to seek extensions of patent terms in the United States and, if available, in other countries where we are prosecuting patents. In the United States, the Drug Price Competition and Patent Term Restoration Act of 1984 permits a patent term extension of up to five years beyond the normal expiration of the patent, which is limited to the approved indication (or any additional indications approved during the period of extension). However, the applicable authorities, including the FDA and the USPTO in the United States, and any equivalent regulatory authority in other countries, may not agree with our assessment of whether such extensions are available, and may refuse to grant extensions to our patents, or may grant more limited extensions than we request. If this occurs, our competitors may be able to take advantage of our investment in development and clinical trials by referencing our clinical and preclinical data and launch their drug earlier than might otherwise be the case.

Intellectual property rights do not necessarily address all potential threats to our business.

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. The following examples are illustrative:

- others may be able to make compounds or formulations that are similar to etripamil or formulations of etripamil or our future product candidates but that are not covered by the claims of any patents, should they issue, that we own or control;
- we or any strategic partners might not have been the first to make the inventions covered by the issued patents or pending patent applications that we own or control;
- we might not have been the first to file patent applications covering certain of our inventions;
- 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 pending patent applications will not lead to issued patents;
- issued patents that we own or control may not provide us with any competitive advantages, or may be held invalid or unenforceable as a result of legal challenges;
- our competitors might conduct research and development activities in the United States and other countries that provide a safe harbor from patent infringement claims for certain research and development activities, as well as in countries where we do not have patent rights and then use the information learned from such activities to develop competitive drugs for sale in our major commercial markets;
- we may not develop additional proprietary technologies that are patentable; and the patents of others may have an adverse effect on our business.

Should any of these events occur, they could have a material adverse effect on our business, financial condition, results of operations and prospects.

We may become involved in lawsuits to protect or enforce our patents or other intellectual property rights, which could be expensive, time consuming and unsuccessful.

Competitors may infringe our issued patents, future trademarks, copyrights or other intellectual property. To counter infringement or unauthorized use, we may be required to file infringement claims, which can be expensive and time-consuming and divert the time and attention of our management and scientific personnel. Any claims we assert against perceived infringers could provoke these parties to assert counterclaims against us alleging that we infringe their patents, trademarks, copyrights or other intellectual property. In addition, in a patent infringement proceeding, there is a risk that a court will decide that a patent of ours is invalid or unenforceable, in whole or in part, and that we do not have the right to stop the other party from using the invention at issue. There is also a risk that, even if the validity of such patents is upheld, the court will construe the patent's claims narrowly or decide that we do not have the right to stop the other party from using the invention at issue on the grounds that our patents do not cover the invention. An adverse outcome in a litigation or proceeding involving our patents could limit our ability to assert our patents against those parties or other competitors, and may curtail or preclude our ability to exclude third parties from making and selling similar or competitive products. Similarly, if we assert trademark infringement claims, a court may determine that the marks we have asserted are invalid or unenforceable, or that the party against whom we have asserted trademark infringement has superior rights to the marks in question. In this case, we could ultimately be forced to cease use of such trademarks.

In any infringement litigation, any award of monetary damages we receive may not be commercially valuable. Furthermore, 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 litigation. In addition, there could be public announcements of the results of hearings, motions or other interim proceedings or developments and if securities analysts or investors perceive these results to be negative, it could have a substantial adverse effect on the price of our common shares. Moreover, there can be no assurance that we will have sufficient financial or other resources to file and pursue such infringement claims, which typically last for years before they are concluded. Some of our competitors may be able to sustain the costs of such litigation or proceedings more effectively than we can because of their greater financial resources and more mature and developed intellectual property portfolios. Even if we ultimately prevail in such claims, the monetary cost of such litigation and the diversion of the attention of our management and scientific personnel could outweigh any benefit we receive as a result of the proceedings. Accordingly, despite our efforts, we may not be able to prevent third parties from infringing, misappropriating or successfully challenging our intellectual property rights. Uncertainties resulting from the initiation and continuation of patent litigation or other proceedings could have a negative impact on our ability to compete in the marketplace.

Third parties may initiate legal proceedings alleging that we are infringing their intellectual property rights, the outcome of which would be uncertain and could have a negative impact on the success of our business.

Our commercial success depends, in part, upon our ability and the ability of future collaborators, if any, to develop, manufacture, market and sell etripamil and any future product candidates and use our proprietary technologies without infringing the proprietary rights and intellectual property of third parties. The biotechnology and pharmaceutical industries are characterized by extensive and complex litigation regarding patents and other intellectual property rights. We may in the future become party to, or be threatened with, adversarial proceedings or litigation regarding intellectual property rights with respect to etripamil and any future product candidates and technology, including interference proceedings, post grant review and inter partes review before the USPTO. Third parties may assert infringement claims against us based on existing patents or patents that may be granted in the future, regardless of their merit. There is a risk that third parties may choose to engage in litigation with us to enforce or to otherwise assert their patent rights against us. Even if we believe such claims are without merit, a court of competent jurisdiction could hold that these third-party patents are valid, enforceable and infringed, which could have a negative impact on our ability to commercialize our current and any future product candidates. In order to successfully challenge the validity of any such U.S. patent in federal court, we would need to overcome a presumption of validity. As this burden is a high one requiring us to present clear and convincing evidence as to the invalidity of any such U.S. patent claim, there is no assurance that a court of competent jurisdiction would invalidate the claims of any such U.S. patent. If we are found to infringe a third party's valid and enforceable intellectual property rights, we could be required to obtain a license from such third party to continue developing, manufacturing and marketing our product candidate(s) and technology. However, we may not be able to obtain any required license on commercially reasonable terms or at all. Even if we were able to obtain a license, it could be non-exclusive, thereby giving our competitors and other third parties access to the same technologies licensed to us, and it could require us to make substantial licensing and royalty payments. We could be forced, including by court order, to cease developing, manufacturing and commercializing the infringing technology or product candidate. In addition, we could be found liable for monetary damages, including treble damages and attorneys' fees, if we are found to have willfully infringed a patent or other intellectual property right. A finding of infringement could prevent us from manufacturing and commercializing etripamil or any future product candidates or force us to cease some or all of our business operations, which could materially harm our business. Claims that we have misappropriated the confidential information or trade secrets of third parties could have a similar negative impact on our business, financial condition, results of operations and prospects. See the section herein titled "Legal Proceedings" for additional information.

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.

A third party may hold intellectual property rights, including patent rights, that are important or necessary to the development of etripamil or any future product candidates. It may be necessary for us to use the patented or proprietary technology of third parties to commercialize our product candidates, in which case we would be required to obtain a license from these third parties. Such a license may not be available on commercially reasonable terms, or at all, and we

could be forced to accept unfavorable contractual terms. If we are unable to obtain such licenses on commercially reasonable terms, our business could be harmed.

We may be subject to claims asserting that our employees, consultants or advisors have wrongfully used or disclosed alleged trade secrets of their current or former employers or claims asserting ownership of what we regard as our own intellectual property.

Many of our employees, consultants or advisors are currently, or were previously, employed at universities or other biotechnology or pharmaceutical companies, including our competitors or potential competitors. Although we try to ensure that our employees, consultants and advisors do not use the proprietary information or know-how of others in their work for us, we may be subject to claims that these individuals or we have used or disclosed intellectual property, including trade secrets or other proprietary information, of any such individual's current or former employer. Litigation may be necessary to defend against these claims. If we fail in defending any such claims, in addition to paying monetary damages, 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.

In addition, we may in the future be subject to claims by our former employees or consultants asserting an ownership right in our patents or patent applications, as a result of the work they performed on our behalf. Although it is our policy to require our employees and contractors who may be involved in the development of intellectual property to execute agreements assigning such intellectual property to us, we may be unsuccessful in executing such an agreement with each party who, in fact, conceives or develops intellectual property that we regard as our own, and we cannot be certain that our agreements with such parties will be upheld in the face of a potential challenge or that they will not be breached, for which we may not have an adequate remedy. The assignment of intellectual property rights may not be self-executing or the assignment agreements may be breached, and we may be forced to bring claims against third parties, or defend claims that they may bring against us, to determine the ownership of what we regard as our intellectual property.

Changes in U.S. patent law or the patent law of other countries or jurisdictions could diminish the value of patents in general, thereby impairing our ability to protect etripamil and any future product candidates.

The United States has recently enacted and implemented wide ranging patent reform legislation. The U.S. Supreme Court has ruled on several patent cases in recent years, 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 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.

We may not be able to protect our intellectual property rights throughout the world, which could negatively impact our business.

Filing, prosecuting and defending patents on product candidates in all countries throughout the world would be prohibitively expensive, and our intellectual property rights in some countries outside the United States could be less extensive than those in the United States. In some cases, we may not be able to obtain patent protection for certain technology outside the United States. In addition, the laws of some foreign countries do not protect intellectual property rights to the same extent as federal and state laws in the United States, even in jurisdictions where we do pursue patent protection. Consequently, we may not be able to prevent third parties from practicing our inventions in all countries outside the United States, even in jurisdictions where we do pursue patent protection or from selling or importing products made using our inventions in and into the United States or other jurisdictions.

Many companies have encountered significant problems in protecting and defending intellectual property rights in foreign jurisdictions. The legal systems of certain countries, particularly certain developing countries, do not favor the enforcement of patents and other intellectual property protection, which could make it difficult for us to stop the infringement of our patents, if pursued and obtained, or marketing of competing products in violation of our proprietary rights generally. Proceedings to enforce our patent rights in foreign jurisdictions could result in substantial costs and divert our efforts and attention from other aspects of our business, could put our patents at risk of being invalidated or interpreted narrowly and our patent applications at risk of not issuing and could provoke third parties to assert claims against us. We may not prevail in any lawsuits that we initiate and the damages or other remedies awarded, if any, may not be commercially meaningful. Accordingly, our efforts to enforce our intellectual property rights around the world may be inadequate to obtain a significant commercial advantage from the intellectual property that we develop or license.

Reliance on third parties requires us to share our proprietary information, which increases the possibility that such information will be misappropriated or disclosed.

Because we rely on third parties to develop and manufacture etripamil and any future product candidates, or if we collaborate with third parties for the development or commercialization of etripamil or any future product candidates, we must, at times, share proprietary information with them. We seek to protect our proprietary technology in part by entering into confidentiality agreements and, if applicable, material transfer agreements, consulting agreements or other similar agreements with our advisors, employees, third-party contractors and consultants prior to beginning research or disclosing proprietary information. These agreements typically limit the rights of the third parties to use or disclose our confidential information. Despite the contractual provisions employed when working with third parties, the need to share confidential information increases the risk that such information become known by our competitors, is inadvertently incorporated into the technology of others, or is disclosed or used in violation of these agreements. Given that our proprietary position is based, in part, on our know-how, a competitor’s discovery of our know-how or other unauthorized use or disclosure could have an adverse effect on our business and results of operations.

In addition, these agreements typically restrict the ability of our advisors, employees, third-party contractors and consultants to publish data potentially relating to our know-how. Despite our efforts to protect our know-how, we may not be able to prevent the unauthorized disclosure or use of our technical know-how by the parties to these agreements. Moreover, we cannot guarantee that we have entered into such agreements with each party that may have or have had access to our confidential information or proprietary technology and processes. Monitoring unauthorized uses and disclosures is difficult, and we do not know whether the steps we have taken to protect our proprietary technologies will be effective. If any of the collaborators, scientific advisors, employees, contractors and consultants who are parties to these agreements breaches or violates the terms of any of these agreements, we may not have adequate remedies for any such breach or violation. Moreover, if confidential information that is licensed or disclosed to us by our partners, collaborators, or others is inadvertently disclosed or subject to a breach or violation, we may be exposed to liability to the owner of that confidential information. Enforcing a claim that a third-party illegally obtained and is using our proprietary information, like patent litigation, is expensive and time consuming, and the outcome is unpredictable. In addition, courts outside the United States are sometimes less willing to protect proprietary information.

Any trademarks we may obtain may be infringed or successfully challenged, resulting in harm to our business.

We expect to rely on trademarks as one means to distinguish any of our product candidates that are approved for marketing from the products of our competitors. We have not yet selected trademarks for etripamil and have not yet begun the process of applying to register trademarks for etripamil or any other product candidate. Once we select trademarks and apply to register them, our trademark applications may not be approved. Third parties may oppose our trademark applications or otherwise challenge our use of the trademarks. In the event that our trademarks are successfully challenged, we could be forced to rebrand our products, 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.

In addition, any proprietary name we propose to use with etripamil or any future product candidate in the United States must be approved by the FDA, regardless of whether we have registered it, or applied to register it, as a trademark. The FDA typically conducts a review of proposed product names, including an evaluation of the potential for confusion with other product names. If the FDA objects to any of our proposed proprietary product names, we may be required to expend significant additional resources in an effort to identify a suitable proprietary product name that would qualify under applicable trademark laws, not infringe the existing rights of third parties and be acceptable to the FDA.

If we are unable to protect the confidentiality of our proprietary information, our business and competitive position would be harmed.

In addition to seeking patent and trademark protection for etripamil and any future product candidate, we also rely on unpatented know-how, technology and other proprietary information, to maintain our competitive position. We seek to protect our proprietary information, in part, by entering into non-disclosure and confidentiality agreements with parties who have access to them, such as our employees, corporate collaborators, outside scientific collaborators, contract manufacturers, consultants, advisors and other third parties. We also enter into confidentiality and invention or patent assignment agreements with our employees and consultants. Despite these efforts, any of these parties may breach the agreements and disclose our proprietary information. Monitoring unauthorized uses and disclosures of our intellectual property is difficult, and we do not know whether the steps we have taken to protect our intellectual property will be effective. In addition, we may not be able to obtain adequate remedies for any such breaches. Enforcing a claim that a party illegally disclosed or misappropriated proprietary information is difficult, expensive and time consuming, and the outcome is unpredictable. In addition, some courts inside and outside the United States are less willing or unwilling to protect trade secrets.

Moreover, our competitors may independently develop knowledge, methods and know-how equivalent to our proprietary information. Competitors could purchase our products and replicate some or all of the competitive advantages we derive from our development efforts for technologies on which we do not have patent protection. If any of our proprietary information were to be lawfully obtained or independently developed by a competitor, we would have no right to prevent them, or those to whom they communicate it, from using that technology or information to compete with us. If any of our proprietary information were to be disclosed to or independently developed by a competitor, our competitive position would be harmed.

We also seek to preserve the integrity and confidentiality of our data and other confidential information by maintaining physical security of our premises and physical and electronic security of our information technology systems. While we have confidence in these individuals, organizations and systems, agreements or security measures may be breached and detecting the disclosure or misappropriation of confidential information and enforcing a claim that a party illegally disclosed or misappropriated confidential information is difficult, expensive and time-consuming, and the outcome is unpredictable. Further, we may not be able to obtain adequate remedies for any breach. In addition, our confidential information may otherwise become known or be independently discovered by competitors, in which case we would have no right to prevent them, or those to whom they communicate it, from using that technology or information to compete with us.

Risks Related to Our Business Operations, Employee Matters and Managing Growth

Our future success depends on our ability to retain key executives and to attract, retain and motivate qualified personnel.

We are highly dependent on our President and Chief Executive Officer, Joseph Oliveto, our Chief Medical Officer, Francis Plat, our Chief Commercial Officer, Lorenz Muller and our Chief Financial Officer, Amit Hasija. Each of them may currently terminate their employment with us at any time. The loss of the services of any of these persons could impede the achievement of our research, development and commercialization objectives. We do not currently maintain “key person” life insurance on the lives of our executives or any of our employees other than on our President and Chief Executive Officer, Joseph Oliveto.

Recruiting and retaining qualified scientific and clinical personnel and, if we progress the development of any of our product candidates, commercialization, manufacturing and sales and marketing personnel, will be critical to our success. The loss of the services of our executive officers or other key employees could impede the achievement of our research, development and commercialization objectives and seriously harm our ability to successfully implement our business strategy. Furthermore, replacing executive officers and key employees may be difficult and may take an extended period of time because of the limited number of individuals in our industry with the breadth of skills and experience required to successfully develop, gain regulatory approval of and commercialize our product candidates. Competition to hire from this limited pool is intense, and we may be unable to hire, train, retain or motivate these key personnel on acceptable terms given the competition among numerous pharmaceutical and biotechnology companies for similar personnel. We also experience competition for the hiring of scientific and clinical personnel from universities and research institutions. In addition, we rely on consultants and advisors, including scientific and clinical advisors, to assist us in formulating our research and development and commercialization strategy. Our consultants and advisors may have commitments under consulting or advisory contracts with other entities that may limit their availability to us. If we are unable to continue to attract and retain high-quality personnel, our ability to pursue our growth strategy will be limited.

We expect to expand our organization, and we may experience difficulties in managing this growth, which could disrupt our operations.

As of December 31, 2020, we had 28 full-time employees. As the clinical development of etripamil progresses and as we expand our pipeline, we may experience significant growth in the number of our employees and the scope of our operations, particularly in the areas of research, drug development, regulatory affairs and, if etripamil or any future product candidates receives marketing approval, sales, marketing and distribution. To manage any future growth, we will be required to continue to implement and improve our managerial, operational and financial systems, expand our facilities and continue to recruit and train additional qualified personnel. Due to our limited financial resources and the limited experience of our management team in managing a company with growth, we may not be able to effectively manage any expansion of our operations or recruit and train additional qualified personnel. Any expansion of our operations may lead to significant costs and may divert our management and business development resources. Any inability to manage growth could delay the execution of our business plans or disrupt our operations.

Our internal computer systems, or those of our collaborators or other contractors or consultants, may fail or suffer security breaches, which could result in a significant disruption of our product development programs and our ability to operate our business effectively.

Our internal computer systems and those of our current and any future collaborators and other contractors or consultants are vulnerable to damage from computer viruses, unauthorized access, natural disasters, terrorism, war and telecommunication and electrical failures. Cyber-attacks are increasing in their frequency, sophistication, and intensity, and have become increasingly difficult to detect. Cyber-attacks could include the deployment of harmful malware, ransomware, denial-of-service attacks, social engineering, and other means to affect service reliability and threaten the confidentiality, integrity, and availability of information. Cyber-attacks also could include phishing attempts or e-mail fraud to cause payments or information to be transmitted to an unintended recipient.

While we have not experienced any significant system failure, accident or security breach to date, if such an event were to occur and cause interruptions in our operations, it could result in a disruption of our development programs and our business operations, whether due to a loss of our trade secrets or other proprietary information or other similar disruptions. For example, the loss of clinical trial data from completed or future clinical trials by us or our CROs could result in delays in our regulatory approval efforts and significantly increase our costs to recover or reproduce the data. Additionally, any such event that leads to unauthorized access, use or disclosure of personal information, including personal information regarding our patients or employees, could harm our reputation, cause us not to comply with federal and/or state breach notification laws and foreign law equivalents and otherwise subject us to liability under laws and regulations that protect the privacy and security of personal information. Security breaches and other inappropriate access can be difficult to detect, and any delay in identifying them may lead to increased harm of the type described above. While we have implemented security measures to protect our information technology systems and infrastructure, such measures may not prevent service interruptions or security breaches that could adversely affect our business and to the extent that any disruption or security breach were to result in a loss of, or damage to, our data or applications, or

inappropriate disclosure of confidential or proprietary information, we could incur liability, our competitive position could be harmed and the further development and commercialization of our product candidates could be delayed.

If we fail to comply with European data protection laws, including the European Union General Data Protection Regulation 2016/679, or GDPR, when appropriate, and any other existing or future data protection regulations, our business, financial condition, results of operations and prospects may be materially adversely affected.

We anticipate seeking regulatory approval for, and commercialize, etripamil for the treatment of PSVT in Europe. We may also elect to do so for future product candidates. We are conducting clinical trial activities in Europe, which will subject us to European data protection laws, including the GDPR. The GDPR establishes requirements applicable to the processing of personal data (i.e., data which identifies an individual or from which an individual is identifiable). The GDPR creates significant and complex compliance burdens for companies such as: limiting permitted processing of personal data to only that which is necessary for specified, explicit and legitimate purposes; requiring the establishment a legal basis for processing personal data; expressly confirming that 'pseudonymized' or key-coded data constitutes personal data to which the GDPR applies; creating obligations for controllers and processors to appoint data protection officers in certain circumstances; increasing transparency obligations to data subjects for controllers (including presentation of certain information in a concise, intelligible and easily accessible form about how their personal data is used and their rights vis-à-vis that data and its use); introducing the obligation to carry out so-called data protection impact assessments in certain circumstances; establishing limitations on collection and retention of personal data through 'data minimization' and 'storage limitation' principles; establishing obligations to implement 'privacy by design'; introducing obligations to honor increased rights for data subjects (such as rights for individuals to be 'forgotten,' rights to data portability, rights to object etc. in certain circumstances); formalizing a heightened and codified standard of data subject consent; establishing obligations to implement certain technical and organizational safeguards to protect the security and confidentiality of personal data; introducing obligations to agree to certain specific contractual terms and to take certain measures when engaging third-party processors and joint controllers; introducing the obligation to provide notice of certain significant personal data breaches to the relevant supervisory authority(ies) and affected individuals; and mandating the appointment of representatives in the United Kingdom and/or European Union in certain circumstances. The processing of "special category personal data", such as health information, may also impose heightened compliance burdens under the GDPR. The GDPR has robust regulatory enforcement and penalties for noncompliance, including fines of up to €20 million or 4% of global annual revenue of any noncompliant company for the preceding financial year, whichever is higher. In addition to administrative fines, a wide variety of other potential enforcement powers are available to competent supervisory authorities in respect of potential and suspected violations of the GDPR, including extensive audit and inspection rights, and powers to order temporary or permanent bans on all or some processing of personal data carried out by noncompliant actors. The GDPR also confers a private right of action on data subjects and consumer associations to lodge complaints with supervisory authorities, seek judicial remedies, and obtain compensation for damages resulting from violations of the GDPR. There may be circumstances under which a failure to comply with GDPR, or the exercise of individual rights under the GDPR, would limit our ability to utilize clinical trial data collected on certain subjects. The GDPR will likely impose additional responsibility and liability in relation to our processing of personal data. This may be onerous and materially adversely affect our business, financial condition, results of operations and prospects.

A particular issue presented by the GDPR is the restriction on transfers of personal data from Europe to the United States and most other countries unless the parties to the transfer have implemented specific safeguards to protect the transferred personal data. One of the primary safeguards allowing U.S. companies to import personal data from Europe is the European Commission's Standard Contractual Clauses and we have relied on Standard Contractual Clauses to comply with the GDPR's restrictions on transfer of personal data out of Europe. However, in July 2020 the Court of Justice of the European Union, or CJEU, in a case known colloquially as "Schrems II" raised questions about whether the Standard Contractual Clauses can lawfully be used for personal data transfers from Europe to the United States or other third countries that are not the subject of an adequacy decision of the European Commission. While the CJEU upheld the adequacy of the Standard Contractual Clauses in principle in Schrems II, it made clear that reliance on those Clauses alone may not necessarily be sufficient in all circumstances. Use of the Standard Contractual Clauses must now be assessed on a case-by-case basis taking into account the legal regime applicable in the destination country, in particular regarding applicable surveillance laws and relevant rights of individuals with respect to the transferred data. In the context of any given transfer, where the legal regime applicable in the destination country may or does conflict with the

intended operation of the Standard Contractual Clauses and/or applicable European law, the decision in Schrems II and subsequent draft guidance from the European Data Protection Board, or EDPB, would require the parties to that transfer to implement certain supplementary technical, organizational and/or contractual measures to rely on the Standard Contractual Clauses as a compliant 'transfer mechanism.' However, the aforementioned draft guidance from the EDPB on such supplementary technical, organizational and/or contractual measures appears to conclude that no combination of such measures could be sufficient to allow effective reliance on the Standard Contractual Clauses in the context of transfers of personal data 'in the clear' to recipients in countries where the power granted to public authorities to access the transferred data goes beyond that which is 'necessary and proportionate in a democratic society' – which may, following the CJEU's conclusions in Schrems II on relevant powers of United States public authorities and commentary in that draft EDPB guidance, include the United States in certain circumstances (e.g., where Section 702 of the US Foreign Intelligence Surveillance Act applies). At present, there are few, if any, viable alternatives to the Standard Contractual Clauses. As such, if we are unable to implement a valid solution for personal data transfers from Europe, including, we will face increased exposure to regulatory actions, substantial fines and injunctions against processing personal data from Europe. Inability to import personal data from Europe may also: restrict our activities in Europe; limit our ability to collaborate with partners as well as other service providers, contractors and other companies subject to European data protection laws; and require us to increase our data processing capabilities in Europe at significant expense. Restrictions on our ability to import personal data from Europe could therefore impact our clinical trial activities in Europe and limit our ability to collaborate with CROs and other third parties subject to European data protection laws. Additionally, other countries outside of Europe have enacted or are considering enacting similar cross-border data transfer restrictions and laws requiring local data residency, which could increase the cost and complexity of delivering our services and operating our business. The type of challenges we face in Europe will likely also arise in other jurisdictions that adopt laws similar in construction to the GDPR or regulatory frameworks of equivalent complexity.

Our employees, principal investigators, consultants and commercial partners may engage in misconduct or other improper activities, including non-compliance with regulatory standards and requirements and insider trading.

We are exposed to the risk of fraud or other misconduct by our employees, principal investigators, consultants and commercial partners. Misconduct by these parties could include intentional failures to comply with FDA regulations or the regulations applicable in other jurisdictions, provide accurate information to the FDA and other regulatory authorities, comply with healthcare fraud and abuse laws and regulations in the United States and abroad, report financial information or data accurately or disclose unauthorized activities to us. In particular, sales, marketing and business arrangements in the healthcare industry are subject to extensive laws and regulations intended to prevent fraud, misconduct, kickbacks, self-dealing and other abusive practices. These laws and regulations restrict or prohibit a wide range of pricing, discounting, marketing and promotion, sales commission, customer incentive programs and other business arrangements. Such misconduct also could involve the improper use of information obtained in the course of clinical trials or interactions with the FDA or other regulatory authorities, which could result in regulatory sanctions and cause serious harm to our reputation. It is not always possible to identify and deter employee misconduct, 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 government investigations or other actions or lawsuits stemming from a failure to comply with these laws or regulations. If any such actions are instituted against us and we are not successful in defending ourselves or asserting our rights, those actions could result in significant civil, criminal and administrative penalties, damages, fines, disgorgement, imprisonment, exclusion from participating in government funded healthcare programs, such as Medicare and Medicaid, 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, contractual damages, reputational harm and the curtailment or restructuring of our operations, any of which could have a negative impact on our business, financial condition, results of operations and prospects.

If we engage in future acquisitions or strategic collaborations, this may increase our capital requirements, dilute our shareholders, cause us to incur debt or assume contingent liabilities and subject us to other risks.

We actively search for and continually evaluate various acquisition and strategic collaboration opportunities, including licensing or acquiring complementary drugs, intellectual property rights, technologies or businesses, as deemed

appropriate to carry out our business plan. Any potential acquisition or strategic partnership may entail numerous risks, including:

- increased operating expenses and cash requirements;
- the assumption of additional indebtedness or contingent liabilities;
- assimilation of operations, intellectual property and drugs of an acquired company, including difficulties associated with integrating new personnel;
- the diversion of our management's attention from our existing drug programs and initiatives in pursuing such a strategic partnership, merger or acquisition;
- retention of key employees, the loss of key personnel, and uncertainties in our ability to maintain key business relationships;
- risks and uncertainties associated with the other party to such a transaction, including the prospects of that party and their existing drugs or product candidates and regulatory approvals; and
- our inability to generate revenue from acquired technology and/or drugs sufficient to meet our objectives in undertaking the acquisition or even to offset the associated acquisition and maintenance costs.

In addition, if we engage in future acquisitions or strategic partnerships, we may issue dilutive securities, assume or incur debt obligations, incur large one-time expenses and acquire intangible assets that could result in significant future amortization expense. Moreover, we may not be able to locate suitable acquisition opportunities, and this inability could impair our ability to grow or obtain access to technology or drugs that may be important to the development of our business.

Risks Related to Ownership of Our Common Shares

The market price of our common shares has been and may continue to be volatile and fluctuate substantially, and you could lose all or part of your investment.

The market price of our common shares has been and may continue to be highly volatile and could be subject to wide fluctuations in price in response to various factors, many of which are beyond our control. Since our initial public offering which occurred in May 2019, through March 1, 2021, the price of our common shares has ranged from $1.70 per share to $27.15 per share. The stock market in general and the market for biopharmaceutical and pharmaceutical companies in particular, has experienced extreme volatility that has often been unrelated to the operating performance of particular companies. As a result of this volatility, you may not be able to sell your common shares at or above the price paid for the shares. In addition to the factors discussed in this "Risk Factors" section and elsewhere in this Annual Report on Form 10-K, the market price for our common shares may be influenced by the following:

- the commencement, enrollment or results of our planned or future clinical trials of etripamil and any future product candidates or those of our competitors;
- the success of competitive drugs or therapies;
- regulatory or legal developments in the United States and other countries;
- the success of competitive products or technologies;
- developments or disputes concerning patent applications, issued patents or other proprietary rights;

- the recruitment or departure of key personnel;
- the level of expenses related to etripamil and any future product candidates or clinical development programs;
- the results of our efforts to discover, develop, acquire or in-license additional product candidates;
- actual or anticipated changes in estimates as to financial results, development timelines or recommendations by securities analysts;
- our inability to obtain or delays in obtaining adequate drug supply for any approved drug or inability to do so at acceptable prices;
- disputes or other developments relating to proprietary rights, including patents, litigation matters and our ability to obtain patent protection for our technologies;
- significant lawsuits, including patent or shareholder litigation;
- variations in our financial results or those of companies that are perceived to be similar to us;
- changes in the structure of healthcare payment systems, including coverage and adequate reimbursement for any approved drug;
- market conditions in the pharmaceutical and biotechnology sectors;
- general economic, political, and market conditions and overall fluctuations in the financial markets in the United States and abroad; and
- investors' general perception of us and our business.

These and other market and industry factors may cause the market price and demand for our common shares to fluctuate substantially, regardless of our actual operating performance, which may limit or prevent investors from selling their shares at or above the price paid for the shares and may otherwise negatively affect the liquidity of our common shares. In addition, the stock market in general, and biopharmaceutical companies in particular, have experienced extreme price and volume fluctuations that have often been unrelated or disproportionate to the operating performance of these companies.

Some companies that have experienced volatility in the trading price of their shares have been the subject of securities class action litigation. Any lawsuit to which we are a party, with or without merit, may result in an unfavorable judgment. We also may decide to settle lawsuits on unfavorable terms. Any such negative outcome could result in payments of substantial damages or fines, damage to our reputation or adverse changes to our business practices. Defending against litigation is costly and time-consuming, and could divert our management's attention and our resources. Furthermore, during the course of litigation, there could be negative public announcements of the results of hearings, motions or other interim proceedings or developments, which could have a negative effect on the market price of our common shares.

Our common shares are thinly traded and our shareholders may be unable to sell their shares quickly or at market price.

Although we have had periods of high volume daily trading in our common shares, generally our shares are thinly traded. As a consequence of this lack of liquidity, the trading of relatively small quantities of shares by our shareholders may disproportionately influence the price of those shares in either direction. The price for our shares could, for example, decline significantly in the event that a large number of our common shares are sold on the market without

commensurate demand, as compared to a seasoned issuer that could better absorb those sales without adverse impact on its share price.

Concentration of ownership of our common shares among our existing executive officers, directors and principal shareholders may prevent new investors from influencing significant corporate decisions.

Based upon our common shares outstanding as of December 31, 2020, our executive officers, directors and shareholders who owned more than 5% of our outstanding common shares, in the aggregate, beneficially owned shares representing 65.2% of our outstanding common shares. If our executive officers, directors and shareholders who owned more than 5% of our outstanding common shares acted together, they may be able to significantly influence all matters requiring shareholder approval, including the election and removal of directors and approval of any merger, consolidation or sale of all or substantially all of our assets. The concentration of voting power and transfer restrictions could delay or prevent an acquisition of our company on terms that other shareholders may desire or result in the management of our company in ways with which other shareholders disagree.

If research analysts do not publish research or reports, or publish unfavorable research or reports, about us, our business or our market, our share price and trading volume could decline.

The trading market for our common shares will be influenced by the research and reports that industry or financial analysts publish about us or our business. Equity research analysts may discontinue research coverage of our common shares, and such lack of research coverage may adversely affect the market price of our common shares. We do not have any control over the analysts or the content and opinions included in their reports. The price of our shares could decline if one or more equity research analysts downgrade our shares or issue other unfavorable commentary or research about us. If one or more equity research analysts ceases coverage of us or fails to publish reports on us regularly, demand for our shares could decrease, which in turn could cause the trading price or trading volume of our common shares to decline.

Because we do not anticipate paying any cash dividends on our share capital in the foreseeable future, capital appreciation, if any, will be your sole source of gain.

You should not rely on an investment in our common shares to provide dividend income. We have never declared or paid cash dividends on our share capital. We currently intend to retain all of our future earnings, if any, to finance the growth and development of our business. In addition, the terms of any future debt agreements or preferred equity may preclude us from paying dividends. As a result, capital appreciation, if any, of our common shares will be your sole source of gain for the foreseeable future. Investors seeking cash dividends should not purchase our common shares.

We have broad discretion in the use of our cash, cash equivalents and short-term investments and may use them in ways in which you do not agree or in ways that do not increase the value of your investment.

Our management has broad discretion in the application of our cash, cash equivalents and short-term investments, and could spend these funds in ways that do not improve our results of operations or enhance the value of our common shares. The failure by our management to apply these funds effectively could result in financial losses that could have a negative impact on our business, cause the price of our common shares to decline and delay the development of our product candidates. Pending their use, we may invest our cash, cash equivalents and short-term investments, in a manner that does not produce income or that loses value.

If we are a passive foreign investment company, there could be adverse U.S. federal income tax consequences to U.S. Holders (as defined below).

Based on the nature and composition of our income, assets, activities and market capitalization for our taxable year ending December 31, 2020, we believe that we may have been classified as a passive foreign investment company, or PFIC, for our taxable year ending December 31, 2020. Based on the expected nature and composition of our income and assets for our taxable year ending December 31, 2021, we expect that we may be classified as a PFIC for our taxable

year ending December 31, 2021. If we are a PFIC for the current taxable year, or any subsequent taxable years, we intend to annually furnish U.S. Holders, upon request, a "PFIC Annual Information Statement," with the information required to allow U.S. Holders to make a "qualified electing fund" election, or "QEF Election" for United States federal income tax purposes. No assurances regarding our PFIC status can be provided for any past, current or future taxable years. The determination of whether we are a PFIC is a fact-intensive determination made on an annual basis and the applicable law is subject to varying interpretation. In particular, the characterization of our assets as active or passive may depend in part on our current and intended future business plans, which are subject to change. In addition, the total value of our assets for PFIC testing purposes may be determined in part by reference to the market price of our common shares from time to time, which may fluctuate considerably. As a result, our PFIC status may change from year to year. Under the income test, our status as a PFIC depends on the composition of our income which will depend on the transactions we enter into in the future and our corporate structure. The composition of our income and assets is also affected by how, and how quickly, we spend the cash we raise in any offering.

If we are a PFIC, U.S. Holders may be subject to adverse U.S. federal income tax consequences, such as ineligibility for any preferential tax rates for individuals on capital gains or on actual or deemed dividends, interest charges on certain taxes treated as deferred, and additional reporting requirements under U.S. federal income tax laws and regulations.

A "U.S. Holder" is a holder of our common shares who, for U.S. federal income tax purposes, is: (i) an individual who is a citizen or resident of the United States; (ii) a corporation, or another entity taxable as a corporation, created or organized in or under the laws of the United States, any state therein or the District of Columbia; (iii) an estate the income of which is subject to U.S. federal income taxation regardless of its source; or (iv) a trust if (1) a U.S. court is able to exercise primary supervision over the administration of the trust and one or more U.S. persons have authority to control all substantial decisions of the trust or (2) the trust has a valid election to be treated as a U.S. person under applicable U.S.Treasury Regulations.

If a U.S. Holder is treated as owning at least 10% of our common shares, such holder may be subject to adverse U.S. federal income tax consequences.

If a U.S. Holder is treated as owning (directly, indirectly or constructively) at least 10% of the value or voting power of our common shares, such U.S. Holder may be treated as a "United States shareholder" with respect to each "controlled foreign corporation" in our group (if any). Because our group includes at least one U.S. subsidiary (Milestone Pharmaceuticals USA Inc.), if we were to form or acquire any non-U.S. subsidiaries in the future, they may be treated as controlled foreign corporations. A United States shareholder of a controlled foreign corporation may be required to annually report and include in its U.S. taxable income its pro rata share of "Subpart F income," "global intangible low-taxed income" and investments in U.S. property by that controlled foreign corporation, regardless of whether that controlled foreign corporation, or we, make any distributions. An individual that is a United States shareholder with respect to a controlled foreign corporation generally would not be allowed certain tax deductions or foreign tax credits that would be allowed to a United States shareholder that is a U.S. corporation. We cannot provide any assurances that we will assist investors in determining whether any non-U.S. subsidiaries that we may form or acquire in the future will be treated as controlled foreign corporations or whether any such investor would be treated as a United States shareholder with respect to any of such controlled foreign corporations. Further, we cannot provide any assurances that we will furnish to any investor information that may be necessary to comply with the reporting and tax paying obligations discussed above. Failure to comply with these reporting obligations may subject a U.S. Holder to significant monetary penalties and may extend the statute of limitations with respect to its U.S. federal income tax return for the year for which reporting was due. U.S. Holders should consult their tax advisors regarding the potential application of these rules to their investment in our common shares.

Future changes to tax laws could materially adversely affect our company and reduce net returns to our shareholders.

Our tax treatment is subject to the enactment of, or changes in, tax laws, regulations and treaties, or the interpretation thereof, tax policy initiatives and reforms under consideration and the practices of tax authorities in jurisdictions in which we operate, including those related to the Organization for Economic Co-Operation and Development's, or OECD, Base Erosion and Profit Shifting, or BEPS, Project, the European Commission's state aid investigations and

other initiatives. Such changes may include (but are not limited to) the taxation of operating income, investment income, dividends received or (in the specific context of withholding tax) dividends paid. We are unable to predict what tax reform may be proposed or enacted in the future or what effect such changes would have on our business, but such changes, to the extent they are brought into tax legislation, regulations, policies or practices, could affect our financial position and overall or effective tax rates in the future in countries where we have operations, reduce post-tax returns to our shareholders, and increase the complexity, burden and cost of tax compliance.

For example, the Tax Act enacted many significant changes to the U.S. tax laws. Future guidance from the Internal Revenue Service and other tax authorities with respect to the Tax Act may affect us, and certain aspects of the Tax Act could be repealed or modified in future legislation. For example, the CARES Act modified certain provisions of the Tax Act. In addition, it is uncertain if and to what extent various states will conform to the Tax Act, the CARES Act or any newly enacted federal tax legislation. Changes in corporate tax rates, the realization of net deferred tax assets relating to our operations, the taxation of foreign earnings, and the deductibility of expenses under the Tax Act or future reform legislation could have a material impact on the value of our deferred tax assets, could result in significant one-time charges, and could increase our future U.S. tax expense. We urge you to consult with your legal and tax advisors with respect to this legislation and the potential tax consequences of investing in or holding our common shares.

Tax authorities may disagree with our positions and conclusions regarding certain tax positions, resulting in unanticipated costs, taxes or non-realization of expected benefits.

A tax authority may disagree with tax positions that we have taken, which could result in increased tax liabilities. For example, the Canadian Revenue Agency, the U.S. Internal Revenue Service or another tax authority could challenge our allocation of income by tax jurisdiction and the amounts paid between our affiliated companies pursuant to our intercompany arrangements and transfer pricing policies, including amounts paid with respect to our intellectual property development. Similarly, a tax authority could assert that we are subject to tax in a jurisdiction where we believe we have not established a taxable connection, often referred to as a "permanent establishment" under international tax treaties, and such an assertion, if successful, could increase our expected tax liability in one or more jurisdictions. A tax authority may take the position that material income tax liabilities, interest and penalties are payable by us, in which case, we expect that we might contest such assessment. Contesting such an assessment may be lengthy and costly and if we were unsuccessful in disputing the assessment, the result could increase our anticipated effective tax rate.

We are an "emerging growth company," and the reduced disclosure requirements applicable to emerging growth companies may make our common shares less attractive to investors.

We are an "emerging growth company," or EGC, as defined in the Jumpstart Our Business Startups Act of 2012, or the JOBS Act, and we intend to take advantage of some of the exemptions from reporting requirements that are applicable to other public companies that are not emerging growth companies, including:

- not being required to comply with the auditor attestation requirements in the assessment of our internal control over financial reporting;
- not being required to comply with any requirement that may be adopted by the Public Company Accounting Oversight Board regarding mandatory audit firm rotation or a supplement to the auditor's report providing additional information about the audit and the financial statements;
- reduced disclosure obligations regarding executive compensation; and
- not being required to hold a nonbinding advisory vote on executive compensation and shareholder approval of any golden parachute payments not previously approved.

We currently take advantage of some or all of these reporting exemptions and may continue to until we are no longer an EGC. We will remain an EGC until the earlier of (i) December 31, 2024, (ii) the last day of the fiscal year in which we have total annual gross revenue of at least $1.07 billion, (iii) the last day of the first fiscal year in which we are deemed

to be a large accelerated filer, which means the market value of our common shares that is held by non-affiliates exceeds $700 million as of the prior June 30th, and (iv) the date on which we have issued more than $1.0 billion in non-convertible debt during the prior three-year period. We cannot predict whether investors will find our common shares less attractive because we will rely on these exemptions. If some investors find our common shares less attractive as a result, there may be a less active trading market for our common shares and our share price may be more volatile.

In addition, under Section 107(b) of the JOBS Act, EGCs can delay adopting new or revised accounting standards until such time as those standards apply to private companies. We have irrevocably elected not to avail ourselves of this exemption from new or revised accounting standards and, therefore, we will be subject to the same new or revised accounting standards as other public companies that are not EGCs.

We are incurring, and expect to continue to incur additional costs as a result of operating as a public company, and our management will be required to devote substantial time to new compliance initiatives.

As a public company, and particularly after we are no longer an EGC, we are incurring, and expect to continue to incur, significant legal, accounting and other expenses that we did not incur as a private company. In addition, the Sarbanes-Oxley Act of 2002, or the Sarbanes-Oxley Act, and rules subsequently implemented by the SEC and The Nasdaq Stock Market LLC have imposed various requirements on public companies, including establishment and maintenance of effective disclosure and financial controls and corporate governance practices. Our management and other personnel need to devote a substantial amount of time to these compliance initiatives. Moreover, these rules and regulations have increased, and will continue to increase, our legal and financial compliance costs and make some activities more time-consuming and costly.

Pursuant to Section 404 of the Sarbanes-Oxley Act, or Section 404, we will be required to furnish a report by our management on our internal control over financial reporting, including an attestation report on internal control over financial reporting issued by our independent registered public accounting firm. However, while we remain an EGC, we will not be required to include an attestation report on internal control over financial reporting issued by our independent registered public accounting firm. To achieve compliance with Section 404 within the prescribed period, we will be engaged in a process to document and evaluate our internal control over financial reporting, which is both costly and challenging. In this regard, we will need to continue to dedicate internal resources, potentially engage outside consultants and adopt a detailed work plan to assess and document the adequacy of internal control over financial reporting, continue steps to improve control processes as appropriate, validate through testing that controls are functioning as documented and implement a continuous reporting and improvement process for internal control over financial reporting. Despite our efforts, there is a risk that neither we nor our independent registered public accounting firm will be able to conclude within the prescribed timeframe that our internal control over financial reporting is effective as required by Section 404. This could result in an adverse reaction in the financial markets due to a loss of confidence in the reliability of our consolidated financial statements.

Because we are a Canadian company, it may be difficult to serve legal process or enforce judgments against us.

We are a domestic filer in the United States; however, we are incorporated and have our corporate headquarters in Canada. In addition, while many of our directors and officers reside in the United States, several of them reside outside of the United States. Accordingly, service of process upon us may be difficult to obtain within the United States. Furthermore, because substantially all of our assets are located outside the United States, any judgment obtained in the United States against us, including one predicated on the civil liability provisions of the U.S. federal securities laws, may not be collectible within the United States. Therefore, it may not be possible to enforce those actions against us.

In addition, it may be difficult to assert U.S. securities law claims in original actions instituted in Canada. Canadian courts may refuse to hear a claim based on an alleged violation of U.S. securities laws against us or these persons on the grounds that Canada is not the most appropriate forum in which to bring such a claim. Even if a Canadian court agrees to hear a claim, it may determine that Canadian law and not U.S. law is applicable to the claim. If U.S. law is found to be applicable, the content of applicable U.S. law must be proved as a fact, which can be a time-consuming and costly process. Certain matters of procedure will also be governed by Canadian law. Furthermore, it may not be possible to

subject foreign persons or entities to the jurisdiction of the courts in Canada. Similarly, to the extent that our assets are located in Canada, investors may have difficulty collecting from us any judgments obtained in the U.S. courts and predicated on the civil liability provisions of U.S. securities provisions.

We are governed by the corporate laws of Québec, which in some cases have a different effect on shareholders than the corporate laws of Delaware.

We are governed by the Business Corporations Act (Québec), or the QBCA, and other relevant laws, which may affect the rights of shareholders differently than those of a company governed by the laws of a U.S. jurisdiction, and may, together with our charter documents, have the effect of delaying, deferring or discouraging another party from acquiring control of us by means of a tender offer, a proxy contest or otherwise, or may affect the price an acquiring party would be willing to offer in such an instance. The material differences between the QBCA and Delaware General Corporation Law, or the DGCL, that may have the greatest such effect include but are not limited to the following: (i) for material corporate transactions (such as mergers and amalgamations, other extraordinary corporate transactions or amendments to our articles), the QBCA generally requires a two-thirds majority vote by shareholders, whereas the DGCL generally only requires a majority vote; and (ii) under the QBCA, a holder of 5% or more of our common shares can requisition a special meeting of shareholders, whereas such right does not exist under the DGCL.

Our bylaws and certain Canadian legislation contain provisions that may have the effect of delaying or preventing certain change in control transactions or shareholder proposals.

Certain provisions of our bylaws and certain Canadian legislation, together or separately, could discourage or delay certain change in control transactions or shareholder proposals.

Our bylaws contain provisions that establish certain advance notice procedures for nomination of candidates for election as directors at shareholders' meetings. The BCA requires that any shareholder proposal that includes nominations for the election of directors must be signed by one or more holders of shares representing in the aggregate not less than 5% of the shares or 5% of the shares of a class or series of shares of the corporation entitled to vote at the meeting to which the proposal is to be presented.

The *Investment Canada Act* requires that a non-Canadian must file an application for review with the Minister responsible for the *Investment Canada Act* and obtain approval of the Minister prior to acquiring control of a "Canadian business" within the meaning of the *Investment Canada Act*, where prescribed financial thresholds are exceeded. Furthermore, limitations on the ability to acquire and hold our common shares may be imposed by the *Competition Act* (Canada). This legislation permits the Commissioner of Competition, or Commissioner, to review any acquisition or establishment, directly or indirectly, including through the acquisition of shares, of control over or of a significant interest in our company. Otherwise, there are no limitations either under the laws of Canada or Quebec, or in our articles on the rights of non-Canadians to hold or vote our common shares.

Any of these provisions may discourage a potential acquirer from proposing or completing a transaction that may have otherwise presented a premium to our shareholders.

ITEM 1B. UNRESOLVED STAFF COMMENTS.

None.

ITEM 2. PROPERTIES.

Our headquarters is currently located in Montréal (Québec), Canada and consists of 7,700 square feet of leased office space under a lease that expires in November 2025. We also have a U.S. subsidiary based in Charlotte, North Carolina. We believe that our facilities are adequate to meet our current needs.

ITEM 3. LEGAL PROCEEDINGS.

From time to time, we may become involved in legal proceedings arising in the ordinary course of our business. We are not currently a party to any material legal proceedings, and we are not aware of any pending or threatened legal proceeding against us that we believe could have an adverse effect on our business, operating results or financial condition.

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 shares began trading on The Nasdaq Global Select Market on May 9, 2019. Our common shares trade under the symbol "MIST". Prior to the commencement of trading on the Nasdaq Global Select Market on May 9, 2019, there was no public market for our common shares.

HOLDERS OF RECORD

As of December 31, 2020, there were 15 holders of record of our common shares, including Cede & Co., a nominee for The Depository Trust Company, or DTC, which holds shares of our common shares on behalf of an indeterminate number of beneficial owners. All of the common shares held by brokerage firms, banks and other financial institutions as nominees for beneficial owners are deposited into participant accounts at DTC, and are considered to be held of record by Cede & Co. as one shareholder. Because many of our shares are held by brokers and other institutions on behalf of shareholders, we are unable to estimate the total number of shareholders represented by these record holders.

Recent Sales of Unregistered Securities

On July 29, 2020, we entered into an Open Market Sale Agreement℠, or the Sales Agreement, with Jefferies LLC or Jefferies with respect to an at-the-market offering program , or the ATM Program, under which we may issue and sell our common shares having an aggregate offering price of up to $50 million through Jefferies as our sales agent or principal. The common shares to be sold under the Sales Agreement, if any, will be offered and sold pursuant to our shelf registration statement on Form S-3 (File No. 333-239318), which was declared effective by the Securities and Exchange Commission on July 6, 2020. We have not sold shares under the ATM program as of the date of this filing.

On October 22, 2020, we entered into an underwriting agreement with Jefferies and Piper Sandler & Co. as representatives of the several underwriters, or collectively, the Underwriters, relating to the issuance and sale of (i) 5,095,897 common shares, without par value, at a price to the public of $5.25 per share, and (ii) pre-funded warrants to purchase 4,761,903 Common Shares at an exercise price equal to $0.01 per share, at a price to the public of $5.24 per common share underlying the pre-funded warrants, or the Offering. Pre-Funded Warrants. The gross proceeds to us from the Offering were $51.7 million, including proceeds from the exercise of the Underwriters' option to purchase additional shares. The securities were offered and sold pursuant to our shelf registration statement on Form S-3 (File No. 333-239318), which was declared effective by the Securities and Exchange Commission on July 6, 2020, a base prospectus dated July 6, 2020 and the related prospectus supplement dated October 22, 2020 and a related registration statement (File No. 333-249623) filed on October 22, 2020 in accordance with Rule 462(b) under the Securities Act of 1933, as amended. The offering closed on October 27, 2020.

Purchase of Equity Securities by the Issuer and Affiliated Purchasers

None.

Securities Authorized for Issuance Under Equity Compensation Plans

Information about securities authorized for issuance under our equity compensation plan is incorporated herein by reference to Item 12 of Part III of this Annual Report on Form 10-K.

ITEM 6. SELECTED FINANCIAL DATA.

Not Applicable.

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

You should read the following discussion and analysis of our financial condition and results of operations together with our consolidated financial statements and related notes included elsewhere in this Annual Report on Form 10-K. This discussion contains forward-looking statements based upon current expectations that involve risks and uncertainties. Our actual results may differ materially from those anticipated in these forward-looking statements as a result of various factors, including those discussed in "Risk Factors" and in other parts of this Annual Report on Form 10-K.

Overview

We are a biopharmaceutical company focused on the development and commercialization of innovative cardiovascular medicines. Our lead product candidate etripamil is a novel, potent and short-acting calcium channel blocker that we designed as a rapid-onset nasal spray to be self-administered by patients. We are developing etripamil to treat paroxysmal supraventricular tachycardia, or PSVT, atrial fibrillation and rapid ventricular rate, or AFib-RVR, and other cardiovascular indications.

Etripamil - Pivotal Clinical Program in PSVT

PSVT is a rapid heart rate condition characterized by episodes of supraventricular tachycardia, or SVT, that start and stop without warning. Episodes of SVT are often experienced by patients with symptoms including palpitations, sweating, chest pressure or pain, shortness of breath, sudden onset of fatigue, lightheadedness or dizziness, fainting and anxiety. Calcium channel blockers have long been approved for the treatment of PSVT as well as other cardiac conditions. Calcium channel blockers available in oral form are frequently used prophylactically to control the frequency and duration of future episodes of SVT. For treatment of episodes of SVT, approved calcium channel blockers are administered intravenously under medical supervision, usually in the emergency department. The combination of convenient nasal-spray delivery, rapid-onset and short duration of action of etripamil has the potential to shift the current treatment paradigm for episodes of SVT away from the burdensome and costly emergency department setting. If approved, we believe that etripamil will be the first self-administered therapy for the rapid termination of episodes of SVT wherever and whenever they occur.

In March 2020, we reported topline results of the first part of the NODE-301 pivotal trial of etripamil for the treatment of PSVT, which is a placebo-controlled Phase 3 safety and efficacy trial. The first part of NODE-301, which enrolled a total of 431 patients across 65 sites in the United States and Canada, did not meet its primary endpoint of time to conversion of SVT to sinus rhythm compared to placebo over the five hour period in which patients wore a cardiac monitor following study drug administration.

In July 2020, we announced that we received guidance from the U.S. Food and Drug Administration, or FDA, on our proposal to alter the size and design of our ongoing RAPID trial as well as the overall program based on the data from the NODE-301 trial. The FDA indicated that the two trials, the RAPID trial and the completed NODE-301 trial, could potentially fulfill the efficacy requirement for our planned NDA for etripamil in patients with PSVT.

Under an updated statistical analysis plan, or SAP, the primary efficacy endpoint for both the RAPID and NODE-301 trials will be defined as time to conversion over the first 30 minutes, with a target p-value of less than 0.05 for each trial. This endpoint supports the desire of patients to rapidly address their PSVT symptoms during an episode and ideally avoid visiting the emergency department. Later and earlier time points will also be assessed as part of secondary analyses to fully characterize the efficacy profile of etripamil.

When employing the updated SAP retrospectively to the NODE-301 data, results in 54% of etripamil patients vs. 35% of placebo patients converted within 30 minutes (HR 1.87, p=0.02). We also discussed the clinical benefit of 54% conversion rate with the FDA. We believe, based on interactions with PSVT treating physicians and cardiovascular thought leaders, that a 50% conversion rate within 60 minutes is a clinically-meaningful outcome given the symptomatic nature of SVT episodes and the lack of approved at-home treatments.

Based on discussions with the FDA regarding maximizing the treatment effect of etripamil, the RAPID trial will allow for repeat administration of study drug (either 70 mg of etripamil or placebo) for patients who have not experienced symptom relief within ten minutes of the first study drug administration. This repeat dose regimen, which is similar to current PSVT treatment practices in the emergency department setting, is tailored to etripamil's pharmacokinetic profile to deliver increased exposure over approximately the first 30 minutes following initial administration. We expect that the repeat administration could benefit a broader group of patients, including those with more persistent episodes.

The RAPID study, which was originally designed to collect double-blind data from randomized patients who had not yet experienced an SVT event after the NODE-301 study reached its target number of adjudicated SVT events, will be amended and expanded to serve as a pivotal efficacy and safety study should the RAPID study meet its primary objective. The study will include the 170 patients who are already enrolled, although many of those patients have been enrolled in the study for more than one year without reporting an SVT event. The study will be completed after a total of 180 confirmed SVT events are reached, including those that have already occurred in the study. Additional patients to be enrolled in the RAPID study will be randomized 1:1.

During the fourth quarter of 2020, we observed delays in our enrollment and clinical trial site startups for the RAPID study. We believe the effects of the COVID-19 pandemic and its impact contributed to such delays. As a result we have taken measures to increase the enrollment of patients by increasing the number of clinical trial sites, including more clinical sites planned in European countries to diversify and better protect the study recruitment against COVID's geographical resurgences. We are also increasing site specific support for clinical trial sites currently open. We will continue to monitor the impact of COVID-19 on the study and expect to continue these enrollment enhancing initiatives throughout 2021. While we monitor the effect of those initiatives, we are maintaining our guidance of achieving topline data from the RAPID trial in late 2021 or early 2022.

The FDA agreed that the single and repeat administrations of etripamil could be pooled and compared to placebo for the primary analysis, resulting in no increase in the study's sample size.

Etripamil - Safety Studies in PSVT

NODE-302 is our Phase 3 open-label safety extension of the NODE-301 trial. Patients who completed NODE-301 could enroll in NODE-302 and receive up to an additional 11 doses of etripamil. NODE-302 is a multi- center, open label study designed to evaluate the safety of etripamil nasal spray when self-administered by patients without medical supervision for spontaneous episodes of SVT in an outpatient setting. Eligibility was also contingent on satisfying all inclusion and exclusion criteria, including not experiencing a serious adverse event related to the study drug or the study procedure that precludes the self-administration of etripamil. We completed NODE-302 in late 2020 with a data set of 245 episodes with 105 patients dosed at least once out of 169 patients enrolled. Trial results will contribute to the etripamil NDA safety database.

NODE-303 is a Phase 3, multi-center, open-label safety trial, evaluating the safety of etripamil when self-administered without medical supervision, and evaluating the treatment safety and efficacy of etripamil on multiple SVT episodes. We originally designed this trial to enroll enough patients to collect data on 1,000 patients taking etripamil in an at-home setting. With the expanded size of the RAPID trial, we expect the size of the NODE-303 study to be reduced. We expect to determine a more accurate sizing of the trial following future discussions with the FDA and other regulatory authorities. Based on a review of the NODE-301 safety data available in June 2019, the FDA and multiple European and Latin American regulatory authorities agreed to allow patient enrollment in NODE-303 without an in-office safety test dose, which was required in the NODE-301 trial, and in a broad patient population including patients taking concomitant beta-blockers and calcium channel blockers.

We are in the process of initiating patient access programs that have as their primary objective providing further access to etripamil to patients who have participated in the clinical development registration trials to treat future SVT episodes. These programs will be tailored to meet the regulatory requirements in the territories in which the clinical sites are located.

Etripamil: Atrial Fibrillation and Rapid Ventricular Rate

As with PSVT, calcium channel blockers are also approved for use in intravenous form for the treatment of some episodes of atrial fibrillation in which patients experience rapid ventricular rates. We began enrollment in a Phase 2 proof-of-concept clinical trial, titled ReVeRA, in the first quarter of 2021 to evaluate the ability of etripamil to reduce ventricular rate in AFib-RVR episodes. The Phase 2 double blind, placebo controlled, proof-of-concept, which will be conducted in Canada in collaboration with the Montreal Heart Institute and other research centers, is expected to enroll approximately 50 patients randomized 1:1 to receive either 70 mg of etripamil nasal spray or placebo. The primary endpoint will assess reduction in ventricular rate, with key secondary endpoints including the time to achieve the maximum reduction in rate and the duration of the effect.The trial is to be conducted in the hospital or emergency department setting under medical supervision. We anticipate reporting data from this study following disclosure of top line results of the RAPID trial.

Operations Overview

Since the commencement of our operations in 2003, we have devoted substantially all of our resources to performing research and development activities in support of our product development efforts, hiring personnel, raising capital to support and expand such activities, providing general and administrative support for these operations and, more recently preparing for commercialization. We operate our business using a significant outsourcing model. As such, our team is composed of a relatively smaller core of employees who direct a significantly larger number of team members who are outsourced in the forms of vendors and consultants to enable execution of our operational plans. We do not currently have any products approved for sale, and we continue to incur significant research and development and general administrative expenses related to our operations.

Since inception, we have incurred significant operating losses. For the years ended December 31, 2020 and 2019, we recorded net losses of $50.0 million and $55.2 million, respectively. As of December 31, 2020, we had an accumulated deficit of $163.5 million. We expect to continue to incur significant losses for the foreseeable future. We anticipate that a substantial portion of our capital resources and efforts in the foreseeable future will be focused on completing the necessary development activities required for obtaining regulatory approval and preparing for potential commercialization of our product candidates. We had $142.3 million of cash, cash equivalents and short-term investments at December 31, 2020.

Although we implemented certain cost-cutting measures in 2020, we nevertheless expect to continue to incur significant expenses and increasing operating losses for at least the next several years. Our net losses may fluctuate significantly from period to period, depending on the timing of our planned clinical trials and expenditures on other research and development activities. We expect our expenses will increase substantially over time as we:

- continue our ongoing and planned development of etripamil, including our Phase 3 clinical trials of etripamil for the treatment of PSVT and our Phase 2 clinical trial of etripamil for the treatment of AFib-RVR;
- seek marketing approvals for etripamil for the treatment of PSVT, AFib-RVR and other cardiovascular indications;
- establish a sales, marketing, manufacturing and distribution capability, either directly or indirectly through third parties, to commercialize etripamil or any future product candidate for which we may obtain marketing approval;
- build a portfolio of product candidates through development, or the acquisition or in-license of drugs, product candidates or technologies;

- initiate preclinical studies and clinical trials for etripamil for any additional indications we may pursue, including the clinical trials for the treatment of atrial fibrillation and rapid ventricular rate as well as other areas of unmet medical need, and for any additional product candidates that we may pursue in the future;
- maintain, protect and expand our intellectual property portfolio;
- hire additional clinical, regulatory and scientific personnel;
- add operational, financial and management information systems and personnel, including personnel to support our product development and planned future commercialization efforts; and
- incur additional legal, accounting, insurance and other expenses associated with operating as a public company.

Recent Developments

Changes to the Board of Directors

On September 21, 2020, our Board of Directors appointed Lisa M. Giles and Robert J. Wills, Ph.D. to the Board of Directors, effective October 1, 2020. Ms. Giles has over 35 years of extensive and significant experience in the pharmaceutical, diagnostic, and device industries, including enterprise strategic planning, R&D and Commercial planning, operations, and business development, and Dr. Wills has over 35 years of extensive and significant experience in the pharmaceutical industry, including preclinical and clinical research and development, business development and strategic partnering.

COVID-19 Business Update

While we are experiencing business or financial impact from the ongoing COVID-19 pandemic at this time, given the global economic slowdown, the overall disruption of global healthcare systems and the other risks and uncertainties associated with the pandemic, our business, financial condition, results of operations and growth prospects could be materially adversely affected. In March 2020, our global workforce transitioned to working remotely and this may otherwise adversely impact our business (see below for discussion on Clinical Development impacts). In addition, working at home policies could increase cybersecurity risk and communication disruptions. Since March of 2020, certain governments have implemented and continually adjusted restrictions as the spread and severity of the COVID-19 virus impacted their territories. We continue to closely monitor the COVID-19 situation as we evolve our business continuity plans and response strategy.

Clinical Development

With respect to clinical development, we have taken measures to maintain patient safety and trial continuity and to preserve study integrity. For our clinical development programs, we have experienced disruptions or delays in our ability to initiate trial sites and enroll and assess patients, and such disruptions or delays may continue. Since our last quarterly filing, the COVID-19 pandemic has impacted our ability to maintain patient enrollment in our NODE-303 study as some of the initiated clinical sites have closed their practices to further enrollment. We believe that the corresponding overall impact on the etripamil PSVT program will be lessened as we downsize the NODE-303 study and allocate resources to the recently initiated RAPID trial. The COVID-19 pandemic has delayed the initiation of many proposed RAPID clinical trial sites as some health care institutions have prioritized their resources for pandemic related activities with some precluding the initiation of new clinical trials. It has also delayed the initiation of enrollment for our ReVeRA trial of etripamil for AFib-RVR due to closures of clinical sites. Given the uncertainty and differing and evolving restrictions applicable to clinical trial sites and participants, additional disruptions and delays are possible. We will continue to monitor the impact of COVID-19 on our planned clinical sites and patient enrollment activities. We could also see an impact on the ability to supply study drug, report trial results, or interact with regulators, ethics committees or other important agencies due to limitations in regulatory authority employee resources or otherwise. In

addition, we rely on contract research organizations or other third parties to assist us with clinical trials, and we cannot guarantee that they will continue to perform their contractual duties in a timely and satisfactory manner as a result of the COVID-19 pandemic. If the COVID-19 pandemic continues and persists for an extended period of time, and if phased reopenings stall or are limited due to continued spread of COVID-19, we could experience further significant disruptions to our clinical development timelines, which would adversely affect our business, financial condition, results of operations and growth prospects.

Corporate Development

We expect that our current operating plan and existing cash and cash equivalents and short-term investments will be sufficient to fund our operations and we do not envision any events or conditions that may cast substantial doubt on our ability to continue as a going concern for at least the next 12 months.

During 2020, we focused our efforts on the development of etripamil PSVT program, and we expect to expand our development activities with respect to our etripamil AFib-RVR program in 2021. Our operating plan may further 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, third-party funding, marketing and distribution arrangements, as well as other collaborations, strategic alliances and licensing arrangements, or any combination of these approaches. Furthermore, the COVID-19 pandemic continues to evolve and has resulted in a significant disruption of global financial markets. It is not possible to reliably estimate the length and severity of this disruption. If the disruption persists and deepens, we could experience an inability to access additional capital, which could in the future negatively affect our operations.

Other Financial and Corporate Impacts

While we expect the COVID-19 pandemic to continue to affect our business operations and financial results, the extent of the impact on our clinical development and regulatory efforts, our corporate development objectives and the value of and market for our common shares, will depend on future developments that are highly uncertain and cannot be predicted with confidence at this time, such as the ultimate duration of the pandemic, travel restrictions, quarantines, social distancing and business closure requirements in the United States, Canada, Europe and other countries, and the effectiveness of actions taken globally to contain and treat the disease.

Components of Results of Operations

Research and Development Expenses

Research and development expenses consist primarily of salaries and fees paid to external service providers and also include personnel costs, including share-based compensation expense and other related compensation expenses. We expense research and development costs in the periods in which they are incurred. Costs for certain development activities are recognized based on an evaluation of the progress to completion of specific tasks using information and data provided to us by our vendors, collaborators and third-party service providers.

To date, substantially all of our research and development expenses have been related to the preclinical and clinical development of etripamil. As we advance etripamil or other product candidates for other indications, we expect to allocate our direct external research and development costs across each of the indications or product candidates. Further, while we expect our research and development costs for the development of etripamil AFib-RVR to increase for initiation of our proof of concept clinical trial, we expect our research and development expenses related to the development of etripamil for PSVT to remain a very large majority of our total research and development expenses. The

following table shows our research and development expenses by type of activity for the years ended December 31, 2020 and 2019, respectively.

(in thousands)	Year Ended December 31, 2020	2019
Clinical and pre-clinical	$ 28,098	$ 34,360
Drug manufacturing and formulation	4,580	5,950
Regulatory and other costs	2,183	2,067
Less: investment tax credits	(373)	(392)
Total research and development expenses	$ 34,488	$ 41,985

We expect our research and development expenses to increase as we continue the development of etripamil and prepare to pursue regulatory approval. The process of conducting the necessary clinical research to obtain regulatory approval is costly and time-consuming and is subject to uncertainties and delays, including as a result of the ongoing COVID-19 pandemic. As a result of the uncertainties discussed above, we are unable to determine the duration and completion costs of our research and development projects or when and to what extent we will generate revenue from the commercialization and sale of our product candidates, if at all.

We recognize the benefit of Canadian research and development tax credits as a reduction of research and development costs for fully refundable investment tax credits.

General and Administrative Expenses

General and administrative expenses include personnel and related compensation costs, expenses for outside professional services, lease expense, insurance expense and other general administrative expenses. Personnel costs consist of salaries, bonuses, benefits, related payroll taxes and share-based compensation. Outside professional services consist of legal, accounting and audit services and other consulting fees.

We expect to continue to incur expenses as a public company, including expenses related to compliance with the rules and regulations of the Securities and Exchange Commission, or SEC, and those of any national securities exchange on which our securities are traded, additional insurance expenses, investor relations activities, and other administrative and professional services.

Commercial Expenses

Commercial expenses consist primarily of personnel and related compensation costs, market and health economic research, and market development activities for PSVT and, to a much lesser extent, AFib-RVR. The focus of these expenses is three-fold: first, we want to leverage rigorous primary and secondary research to fully understand our target disease states from the perspective of the patient, healthcare provider, and payor; second, we want to understand and document the burden of disease posed by PSVT from an epidemiology, healthcare resource use, and cost perspective; and third, we want to engage our target patient, physician, and payor stakeholders with evidence-based and compliant educational materials that serve to increase the awareness and understanding of the impact of PSVT on patients and the overall healthcare system.

Starting approximately one year before we file our new drug application, or NDA with the FDA, we anticipate our commercial expenses will increase substantially as we invest in the infrastructure, personnel, and operational expenses required to launch our first product in the United States, if approved.

Interest Income

Interest income primarily consists of interest income from our cash equivalents and short-term investments.

Results of Operations

Comparison of the Years Ended December 31, 2020 and 2019

The following table summarizes our results of operations:

(in thousands)	Year ended December 31, 2020	2019	$Change	% Change
Operating expenses				
Research and development, net of tax credits	34,488	41,985	(7,497)	(18)%
General and administrative	10,285	7,004	3,281	47 %
Commercial	5,937	8,892	(2,955)	(33)%
Total operating expenses	50,710	57,881	(7,171)	(12)%
Loss from operations	(50,710)	(57,881)	7,171	(12)%
Interest income, net of bank charges	726	2,596	(1,870)	(72)%
Loss and comprehensive loss before income taxes	(49,984)	(55,285)	5,301	(10)%
Income tax recovery	(17)	(56)	39	(70)%
Net loss and comprehensive loss	(49,967)	(55,229)	5,262	(10)%

Research and Development Expenses

Research and development, or R&D expenses decreased by $7.5 million, or 18%, for the year ended December 31, 2020 compared to the year ended December 31, 2019. This decrease was due to the conclusion of the NODE 301 Part 1 study in the first quarter of 2020 and the RAPID Phase 3 study initiated only in late 2020. Spending was primarily related to advancing our Phase 3 efficacy and safety trials in etripamil for the treatment of PSVT. We spent $21.5 million on these programs in 2020 and $28.8 million in 2019. We recorded personnel and related R&D costs of $13.4 million in 2020 and $13.5 million in 2019, including non-cash compensation costs related to share-based compensation expense. We also recognized $0.4 million of R&D investment tax credits provided by the provincial government of Québec for the years ended December 31, 2020 and 2019. Tax credits are recorded as a reduction of our R&D expenses.

General and Administrative Expenses

General and administrative expenses increased by $3.3 million, or 47% for the year ended December 31, 2020 compared to the year ended December 31, 2019. Following our initial public offering, or IPO, in May 2019, insurance costs increased to support risk management activities as a public company. In addition, we incurred increased spending related to consulting, recruiting and professional fees to support the increased compliance requirements of being a public company. Additionally, during the year ended December 31, 2020, compensation and related personnel costs increased when compared to the same period in 2019 due to an increase in administrative headcount, including non-cash compensation cost related to share-based compensation expense.

Commercial Expenses

Commercial expenses decreased by $3.0 million, or 33%, for the year ended December 31, 2020 when compared to the same period in 2019. We reduced operating expenses in the second quarter of 2020 in order to focus our efforts on an optimized clinical development pathway for etripamil. The cuts primarily affected pre-commercialization activities.

Interest Income, Net

Interest income, net of bank charges was $0.7 million and $2.6 million for the years ended December 31, 2020 and 2019, respectively. The reduction in interest income is mainly a result of lower interest rates earned on investments in 2020 when compared to 2019 and of lower cash balances in 2020 compared to the same period in 2019.

Net Loss

For the foregoing reasons, we had net losses of $50.0 million and $55.2 million for the years ended December 31, 2020 and 2019, respectively.

Liquidity and Capital Resources

Sources of Liquidity

Prior to the IPO, we financed our operations primarily through sales of our convertible preferred shares to accredited investors generating net proceeds of $138.8 million. In May 2019, we received net proceeds of $85.4 million from the IPO.

We have incurred operating losses and experienced negative operating cash flows since our inception, and we anticipate to continue to incur losses for at least the next several years. As of December 31, 2020, we had cash, cash equivalents and short-term investments of $142.3 million and an accumulated deficit of $163.5 million.

In July 2020, we entered into a securities purchase agreement with affiliates of RTW Investments LP, an existing shareholder (the Purchasers), to sell and issue to the Purchasers in a private placement, pre-funded warrants to purchase up to an aggregate of 6,655,131 of the our common shares, at a purchase price of $3.7465 per pre-funded warrant for aggregate proceeds of $25 million before deducting offering expenses. The private placement closed on July 24, 2020.

On July 29, 2020, we entered into the Sales Agreement with Jefferies with respect to the ATM Program, under which we may issue and sell our common shares having an aggregate offering price of up to $50 million through Jefferies as our sales agent or principal. We have not yet sold any common shares under the ATM Program.

In addition, on October 22, 2020, we entered into an underwriting agreement with Jefferies and Piper Sandler & Co. as representatives of the Underwriters relating to the issuance and sale of (i) 5,095,897 common shares, without par value, at a price to the public of $5.25 per share, and (ii) pre-funded warrants to purchase 4,761,903 common shares at an exercise price equal to $0.01 per share, at a price to the public of $5.24 per Common Share underlying the pre-funded warrants. The gross proceeds were $51.7 million before deducting offering expenses, including proceeds from the exercise of the Underwriters' option to purchase additional shares. The securities were offered and sold pursuant to a base prospectus dated July 6, 2020 and the related prospectus supplement dated October 22, 2020 and a related registration statement (File No. 333-249623) filed on October 22, 2020 in accordance with Rule 462(b) under the Securities Act of 1933, as amended. The offering closed on October 27, 2020.

We have evaluated whether material uncertainties exist relating to clinical trials, the COVID-19 pandemic and the impact on market conditions. The COVID-19 pandemic has had an impact on our business, operations and clinical development timelines. Government orders and restrictions in order to control the spread of the disease have impacted patient recruitment, enrollment and follow-up visits at clinical sites. At the date of the publication of our quarterly report, it is not possible to reliably estimate the length and severity of these developments. We expect that our current operating plan, existing cash, cash equivalents, short-term investments and access to financing sources to be sufficient to fund our operations and determined that there are no events or conditions that may cast substantial doubt on our ability to continue as a going concern for at least the next 12 months from the date of this filing.

Funding Requirements

We use our cash primarily to fund research and development expenditures. We expect our research and development expenses to increase as we continue the development of etripamil and prepare to pursue regulatory approval. We expect to incur an increase in general and administrative expenses notwithstanding our temporary salary reductions and other measures implemented in June 2020, and an increase in expenses related to commercial activities in 2021 as we focus our efforts on the clinical pathway and potential commercialization of etripamil. We expect to incur increasing operating losses for the foreseeable future as we continue the clinical development of our product candidate. At this time, due to

the inherently unpredictable nature of clinical development, we cannot reasonably estimate the costs we will incur and the timelines that will be required to complete development, obtain marketing approval, and commercialize etripamil or any future product candidates, if at all. For the same reasons, we are also unable to predict when, if ever, we will generate revenue from product sales or whether, or when, if ever, we may achieve profitability. Clinical and preclinical development timelines, the probability of success, and development costs can differ materially from expectations.

In addition, we have exclusive development and commercialization rights for etripamil for all indications that we may pursue and as such have the potential to license development and or commercialization rights for etripamil to a potential partner. We plan to establish commercialization and marketing capabilities using a direct sales force to commercialize etripamil in the United States. Outside of the United States, we are considering commercialization strategies that may include collaborations with other companies. For other new product candidates, our efforts are focused on licensing development and/or commercialization rights from potential partners. In the case of either in-licensing or out-licensing, we cannot forecast when such arrangements will be secured, if at all, and to what degree such arrangements would affect our development and commercialization plans and capital requirements.

The timing and amount of our operating expenditures will depend largely on:

- the timing, progress and results of our ongoing and planned clinical trials and other development activities of etripamil in PSVT, AFib-RVR and in other cardiovascular indications;
- the scope, progress, results and costs of preclinical development, laboratory testing and clinical trials of etripamil for additional indications or any future product candidates that we may pursue;
- our ability to establish collaborations on favorable terms, if at all;
- the ability of vendors and third-party service providers to accurately forecast expenses and deliver on expectations;
- the costs, timing and outcome of regulatory review of etripamil and any future product candidates;
- the costs and timing of future commercialization activities, including product manufacturing, marketing, sales and distribution, for etripamil and any future product candidates for which we receive marketing approval;
- the revenue, if any, received from commercial sales of etripamil and any future product candidates for which we receive marketing approval;
- the costs and timing of preparing, filing and prosecuting patent applications, maintaining and enforcing our intellectual property rights and defending any intellectual property-related claims; and
- the extent to which we acquire or in-license other product candidates and technologies.

Until such time, if ever, as we can generate substantial revenue from product sales, we expect to fund our operations and capital funding needs through equity and/or debt financing. We may also consider entering into collaboration arrangements or selectively partnering for clinical development and commercialization. The sale of additional equity would result in additional dilution to our shareholders. The incurrence of debt financing would result in debt service obligations and the instruments governing such debt could provide for operating and financing covenants that restrict our operations or our ability to incur additional indebtedness or pay dividends, among other items. In addition, the COVID-19 pandemic continues to rapidly evolve and has already resulted in a significant disruption of global financial markets. If the disruption persists and deepens, we could experience an inability to access additional capital, which could in the future negatively affect our operations. If we are not able to secure adequate additional funding, we may be forced to make reductions in spending, extend payment terms with suppliers, liquidate assets where possible, and/or suspend or curtail planned programs. Any of these actions could materially and adversely affect our business, financial condition, results of operations and prospects.

Cash Flows

The following table summarizes our cash flows for the periods indicated:

(in thousands)	Year ended December 31, 2020	2019	$ Change	% Change
Net cash (used in) provided by:				
Operating activities	(50,732)	(51,152)	420	(0.82)%
Investing activities	(70,000)	(384)	(69,616)	18,129.17 %
Financing activities	73,224	85,407	(12,183)	(14.26)%
Net increase (decrease) in cash and cash equivalents during the period	(47,508)	33,871	(81,379)	

Operating Activities

In 2020, we used $50.7 million of cash in operating activities, which consisted of a net loss of $50.0 million and a net change of $5.8 million in our net operating liabilities and offset by non-cash charges of $5.0 million mainly related to share-based compensation expense for grants to employees, board directors and consultants. The change in our net operating assets and liabilities was mainly due to a decrease of $2.1 million for accounts payable and accrued liabilities and an increase of $3.6 million for prepaid expenses.

In 2019, we used $51.2 million of cash in operating activities, which consisted of a net loss of $55.2 million offset by a net change of $2.9 million in our net operating assets and non-cash charges of $1.2 million. The non-cash charges primarily consist of share-based compensation expense for grants to employees. The change in our net operating assets and liabilities was primarily due to a net increase of $3.5 million for accounts payable, a net decrease of $0.2 million for research and development tax credits, interest and sales tax receivable and offset by an increase of $0.5 million for prepaid expenses.

Investing Activities

In 2020, we used $90.0 million of cash from the acquisition of short-term investments and we received $20.0 million of cash from maturities. In 2019, there was a net use of cash of $0.4 million mainly related to cash used for the acquisition of property and equipment. In 2019, short-term investment acquisitions used $35.0 million in cash and provided the same amount of maturities leaving a balance of nil in short-term investments.

Financing Activities

In 2020, our financing activities provided $73.2 million which consisted primarily of $24.8 million of net proceeds from the private placement of pre-funded warrants to existing shareholders in July 2020, $48.1 million of net proceeds from an offering of common shares and pre-funded warrants in October 2020. In 2019, the IPO provided net cash consideration of $85.4 million.

Off-Balance Sheet Arrangements

We have not entered into any off-balance sheet arrangements, as defined in the rules and regulations of the SEC.

Contractual Obligations

We enter into contracts in the normal course of business with clinical research organizations, or CROs, contract manufacturing organizations, or CMOs, and other third parties for clinical trials, preclinical research studies and testing and manufacturing services. These contracts are generally cancelable at our option with various notice requirements as defined in the contract. Payments due upon cancellation consist of payments for services provided or expenses incurred,

including noncancelable obligations of our service providers, up to and through the date of cancellation. These payments are not included as the amount and timing of these payments are not known.

Critical Accounting Policies and Estimates

Our management's discussion and analysis of our financial condition and results of operations is based on our audited consolidated financial statements as at December 31, 2020, which have been prepared in accordance with United States generally accepted accounting principles, or U.S. GAAP and on a basis consistent with those accounting principles followed by us. The preparation of these audited consolidated financial statements requires our management to make judgments and estimates that affect the reported amounts of assets and liabilities and the disclosure of contingent assets and liabilities at the date of the financial statements, as well as the reported revenue generated and expenses incurred during the reporting periods. Our estimates are based on our historical experience and on various other factors that we believe are reasonable under the circumstances, the results of which form the basis for making judgments about the carrying value of assets and liabilities that are not readily apparent from other sources. Significant estimates and judgments include, but are not limited to, research and development tax credits recoverable, research and development expenses, and share-based compensation. Accordingly, actual results may differ from these judgments and estimates under different assumptions or conditions and any such differences may be material. We believe that the accounting policies discussed below are critical to understanding our historical and future performance, as these policies relate to the more significant areas involving management's judgments and estimates.

Effective January 1, 2019, we adopted ASC Topic 842, Leases, and changed the manner in which it accounts for leases under the new standard. For a description of this critical accounting policy and the impact of the change, see Note 4 of our consolidated financial statements.

a) Research & Development Expenses — Accruals and Tax Credits

Research and development costs are charged against income in the period of expenditure. Our research and development costs consist primarily of salaries and fees paid to CROs and to CMO.

Clinical trial expenses include direct costs associated with CROs, direct CMO costs for the formulation and packaging of clinical trial material, as well as investigator and patient-related costs at sites at which our trials are being conducted. Direct costs associated with our CROs and CMOs are generally payable on a time-and-materials basis, or when milestones are achieved. The invoicing from clinical trial sites can lag several months. We record expenses for our clinical trial activities performed by third parties based upon estimates of the percentage of work completed of the total work over the life of the individual trial in accordance with agreements established with CROs and clinical trial sites. We determine the estimates through discussions with internal clinical personnel, CROs and CMOs as to the progress or stage of completion of trials or services and the agreed-upon fee to be paid for such services based on facts and circumstances known to us as of each consolidated balance sheet date. The actual costs and timing of clinical trials are highly uncertain, subject to risks and may change depending upon a number of factors, including our clinical development plan. If the actual timing of the performance of services of the level of effort varies from the estimate, we will adjust the accrual accordingly. Adjustments to prior period estimates have not been material. We recognize the benefit of Canadian research and development tax credits as a reduction of research and development costs for fully refundable investment tax credits and as a reduction of income taxes for investment tax credits that can only be claimed against income taxes payable when there is reasonable assurance that the claim will be recovered.

b) Leases

Our leases are presented based on ASC 842, using the required modified retrospective approach and utilizing the effective date as its date of initial application.

At the inception of an arrangement, the Company determines whether the arrangement is or contains a lease based on the unique facts and circumstances present in the arrangement. Leases with a term greater than one year are recognized on the

balance sheet as right-of-use assets and short-term and long-term lease liabilities, as applicable. The Company does not have financing leases.

Operating lease liabilities and their corresponding right-of-use assets are initially 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 lease contracts is typically not readily determinable. As a result, the Company utilizes its incremental borrowing rate to discount lease payments, which reflects the fixed rate at which the Company 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. Prospectively, the Company will adjust the right-of-use assets for straight-line rent expense or any incentives received and remeasure the lease liability at the net present value using the same incremental borrowing rate that was in effect as of the lease commencement or transition date.

We elected not to recognize leases with an original term of one year or less on the balance sheet. We typically only include an initial lease term in its assessment of a lease arrangement. Options to renew a lease are not included in the our assessment unless there is reasonable certainty that the Company will renew.

c) Share-Based Compensation

We recognize compensation costs related to share options granted to employees, consultants and directors based on the estimated fair value of the awards on the date of grant. We estimate the grant date fair value, and the resulting share-based compensation expense, using the Black-Scholes option-pricing model. This Black-Scholes option pricing model uses various inputs to measure fair value, including estimated fair value of our underlying common shares at the grant date, expected term, estimated volatility, risk-free interest rate and expected dividend yields of our common shares. The grant date fair value of the share-based awards is recognized on a straight-line basis over the requisite service periods, which are generally the vesting period of the respective awards. Forfeitures are accounted for as they occur.

As there had been no public market for our common shares prior to May 13, 2019, the estimated fair value of our common shares prior to that date was determined by our board of directors as of the date of each option grant, with input from management, considering third-party valuations of our common shares as well as our board of directors' assessment of additional objective and subjective factors that it believed were relevant and which may have changed from the date of the most recent third-party valuation through the date of the grant. These third-party valuations were performed in accordance with the guidance outlined in the American Institute of Certified Public Accountants' Accounting and Valuation Guide, *Valuation of Privately-Held-Company Equity Securities Issued as Compensation*. The assumptions underlying these valuations represent management's best estimates, which involve inherent uncertainties and the application of management judgment. As a result, if factors or expected outcomes change and we use significantly different assumptions or estimates, our share-based compensation expense could be materially different. Following the completion of our initial public offering on May 13, 2019, we have determined the per share fair value of our common shares based on the closing price of our common shares as reported by The Nasdaq Stock Market on the date of grant.

The following table summarizes, by grant date, the number of underlying common shares and the associated per-share exercise price, which was the fair value per share as determined by our board of directors on the applicable grant date, for share options granted during the years ended December 31, 2019 and 2020:

	Number of Common Shares Subject to Options Granted	Exercise Price Per Common Share	Estimated Fair Value per Common Share at Grant Date	Estimated Per-Share Fair Value of Options
February 18, 2019	31,018	$ 9.415	$ 9.415	$ 6.655
March 9, 2019	33,086	$ 9.415	$ 9.415	$ 6.644
March 20, 2019	52,638	$ 9.415	$ 9.415	$ 6.714
May 8, 2019	46,998	$ 15.000	$ 15.000	$ 10.773
August 8, 2019	23,620	$ 15.870	$ 15.870	$ 11.125
September 9, 2019	167,000	$ 22.450	$ 22.450	$ 15.623
September 16, 2019	3,760	$ 21.280	$ 21.280	$ 14.851
October 31, 2019	3,760	$ 19.140	$ 19.140	$ 13.305
November 12, 2019	42,000	$ 17.780	$ 17.780	$ 12.160
January 6, 2020	13,000	$ 17.000	$ 17.000	$ 11.948
January 23, 2020	748,400	$ 21.480	$ 21.480	$ 15.248
February 10, 2020	3,760	$ 21.730	$ 21.730	$ 15.390
June 5, 2020	690,500	$ 3.740	$ 3.740	$ 2.610
June 26, 2020	11,000	$ 3.850	$ 3.850	$ 2.680
June 29, 2020	7,800	$ 3.830	$ 3.830	$ 2.740
October 1, 2020	60,000	$ 7.100	$ 7.100	$ 5.200

The intrinsic value of all outstanding options as of December 31, 2020 was $11.8 million, based on the fair value of our common shares of $6.70 per share at December 31, 2020, of which $7.9 million related to vested options and $3.9 million related to unvested options.

Recent Accounting Pronouncements

Refer to Note 2, “Summary of Significant Accounting Policies,” in the accompanying notes to our audited consolidated financial statements for a discussion of recent accounting pronouncements.

Emerging Growth Company Status

The Jumpstart Our Business Startups Act of 2012 permits an “emerging growth company” such as us to take advantage of an extended transition period to comply with new or revised accounting standards applicable to public companies until those standards would otherwise apply to private companies. We have irrevocably elected to “opt out” of this provision and, as a result, we comply with new or revised accounting standards when they are required to be adopted by public companies that are not emerging growth companies.

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

Quantitative and Qualitative Disclosures about Market Risk

We are exposed to market risks in the ordinary course of our business. These risks primarily relate to interest rate risks. We had cash and cash equivalents and short-term investments of $142.3 million and $119.8 million as of December 31, 2020 and 2019, respectively, which consist primarily of bank deposits and guaranteed investment certificates. The primary objective of our investment activities is to preserve principal and liquidity while maximizing income without significantly increasing risk. We do not enter into investments for trading or speculative purposes. Due to the short-term nature of our investment portfolio, we do not believe an immediate 10% increase or decrease in interest rates would have a material effect on the fair market value of our portfolio, and accordingly we do not expect our operating results or cash flows to be materially affected by a sudden change in market interest rates.

We undertake certain transactions in Canadian dollars and as such are subject to risk due to fluctuations in exchange rates. Canadian dollar denominated payables are paid at the converted rate as due. We do not use derivative instruments to hedge exposure to foreign exchange rate risk due to the low volume of transactions denominated in foreign currencies. At December 31, 2020 and 2019, our net monetary exposure denominated in Canadian dollars was $0.2 million and $1.5 million, respectively.

Our operating results and financial position are reported in U.S. dollars in our financial statements. The fluctuation of the Canadian dollar in relation to the U.S. dollar might, consequently, have an impact upon our loss and may also affect the value of our assets and the amount of shareholders' equity. We do not believe that inflation and changing prices had a significant impact on our results of operations for any periods presented herein.

ITEM 8. FINANCIAL STATEMENTS

Report of Independent Registered Public Accounting Firm

To the Shareholders and Board of Directors of Milestone Pharmaceuticals Inc.

Opinion on the Financial Statements

We have audited the accompanying consolidated balance sheets of Milestone Pharmaceuticals Inc. and its subsidiary (together, the Company) as of December 31, 2020 and 2019, and the related consolidated statements of loss and comprehensive loss, shareholders' equity and convertible preferred shares and of cash flows for the years then ended, including 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 as of December 31, 2020 and 2019, and the results of its operations and its cash flows for the years then ended in conformity with accounting principles generally accepted in the United States of America.

Change in Accounting Principle

As discussed in Note 4 to the consolidated financial statements, the Company changed the manner in which it accounts for leases in 2019.

Basis for Opinion

These consolidated financial statements are the responsibility of the Company's management. Our responsibility is to express an opinion on the Company's consolidated 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 of these consolidated financial statements 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 consolidated 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 consolidated 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 consolidated 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 consolidated financial statements. We believe that our audits provide a reasonable basis for our opinion.

/s/ PricewaterhouseCoopers LLP
Montréal, Québec, Canada
March 29, 2021

We have served as the Company's auditor since 2016.

Milestone Pharmaceuticals Inc.
Consolidated Balance Sheets
(in thousands of US dollars, except share data)

	December 31, 2020	December 31, 2019
Assets		
Current assets		
Cash and cash equivalents	$ 72,310	$ 119,818
Short-term investments (note 3)	70,000	—
Research and development tax credits receivable	725	578
Prepaid expenses	5,428	1,845
Other receivables	223	258
Total current assets	148,686	122,499
Operating lease right-of-use assets (note 4)	980	524
Property and equipment (note 5)	308	405
Total assets	$ 149,974	$ 123,428
Liabilities		
Current liabilities		
Accounts payable and accrued liabilities (note 6)	$ 5,914	$ 7,997
Current portion of operating lease liabilities	245	330
Total current liabilities	6,159	8,327
Operating lease liabilities	696	184
Total liabilities	6,855	8,511
Shareholders' Equity (note 1, note 7)		
Share capital		
Common shares, no par value, unlimited shares authorized, 29,827,997 shares issued and outstanding as of December 31, 2020, 24,505,748 shares issued and outstanding as of December 31, 2019.	251,682	226,245
Pre-funded warrants - 11,417,034 issued and outstanding at December 31, 2020, nil at December 31, 2019	48,007	—
Additional paid-in capital	8,530	3,805
Cumulative translation adjustment	(1,634)	(1,634)
Accumulated deficit	(163,466)	(113,499)
Total shareholders' equity	143,119	114,917
Total liabilities and shareholders' equity	$ 149,974	$ 123,428

The accompanying notes are an integral part of these consolidated financial statements.

Milestone Pharmaceuticals Inc.
Consolidated Statements of Loss and Comprehensive Loss
(in thousands of US dollars, except share and per share data)

	Year ended December 31,	
	2020	**2019**
Operating expenses		
Research and development, net of tax credits (note 10)	$ 34,488	$ 41,985
General and administrative	10,285	7,004
Commercial	5,937	8,892
Loss from operations	$ (50,710)	$ (57,881)
Interest income, net of bank charges	726	2,596
Loss before income taxes	(49,984)	(55,285)
Income tax recovery (note 9)	(17)	(56)
Net loss and comprehensive loss for the year	$ (49,967)	$ (55,229)
Weighted average number of shares and pre-funded warrants outstanding, basic and diluted	29,344,993	15,784,750
Net loss per share, basic and diluted (note 8)	$ (1.70)	$ (3.50)

The accompanying notes are an integral part of these consolidated financial statements.

Milestone Pharmaceuticals Inc.
Consolidated Statements of Shareholders' Equity and Convertible Preferred Shares
(in thousands of US dollars, except share data)

	Common Shares		Convertible Preferred Shares												Pre-funded warrants					
			Class A1		Class A2		Class B		Class C		Class D1		Class D2							
	Number of shares	Amount	Number of shares	Amount	Number of shares	Amount	Number of shares	Amount	Number of shares	Amount	Number of shares	Amount	Number of shares	Amount	Number of warrants	Amount	Additional paid-in capital	Cumulative translation adjustment	Accumulated deficit	Total
Balance as of December 31, 2018	596,787	$ 2,039	372,211	$ 2,027	2,443,914	$ 12,643	2,830,907	$ 17,198	3,786,878	$ 27,236	6,893,236	64,719	1,223,656	14,935	—	$ —	$ 2,655	$ (1,634)	$ (58,270)	$ 83,54
Transactions in 2019																				
Net loss and comprehensive loss	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	(55,229)	(55,22
Exercise of stock options (note 7)	33,159	85	—	—	—	—	—	—	—	—	—	—	—	—	—	—	(41)	—	—	4
Share-based compensation (note 7)	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	1,191	—	—	1,19
Initial public offering (note 7)	6,325,000	85,363	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	85,36
Preferred share conversion (note 7)	17,550,802	138,758	(372,211)	(2,027)	(2,443,914)	(12,643)	(2,830,907)	(17,198)	(3,786,878)	(27,236)	(6,893,236)	(64,719)	(1,223,656)	(14,935)	—	—	—	—	—	–
Balance as of December 31, 2019	24,505,748	$226,245	—	$ —	—	$ —	—	$ —	—	$ —	—	$ —	—	$ —	—	$ —	$ 3,805	$ (1,634)	$ (113,499)	$114,91
Balance as of December 31, 2019	24,505,748	$226,245	—	$ —	—	$ —	—	$ —	—	$ —	—	$ —	—	$ —	—	$ —	$ 3,805	$ (1,634)	$ (113,499)	$114,91
Transactions in 2020																				
Net loss and comprehensive loss	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	(49,967)	(49,96
Exercise of stock options (note 7)	226,352	520	—	—	—	—	—	—	—	—	—	—	—	—	—	—	(220)	—	—	30
Share-based compensation (note 7)	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	4,945	—	—	4,94
Private Placement (note 7)	—	—	—	—	—	—	—	—	—	—	—	—	—	—	6,655,131	24,771	—	—	—	24,77
Public Offering	5,095,897	24,917	—	—	—	—	—	—	—	—	—	—	—	—	4,761,903	23,236	—	—	—	48,15
Balance as of December 31, 2020	29,827,997	$ 251,682	—	$ —	—	$ —	—	$ —	—	$ —	—	$ —	—	$ —	11,417,034	$ 48,007	$ 8,530	$ (1,634)	$ (163,466)	$ 143,11

The accompanying notes are an integral part of these consolidated financial statements.

Milestone Pharmaceuticals Inc.
Consolidated Statements of Cash Flows
(in thousands of US dollars)

	Year ended December 31,	
	2020	**2019**
Cash flows from		
Operating activities		
Net loss for the year	$ (49,967)	$ (55,229)
Adjustments to reconcile net loss to net cash used in operating activities:		
Amortization of property and equipment (note 5)	97	38
Share-based compensation expense (note 7)	4,945	1,191
Changes in operating assets and liabilities:		
Other receivables	35	119
Research and development tax credits receivable	(147)	(288)
Prepaid expenses	(3,583)	(447)
Operating lease right of use asset, net	(29)	—
Accounts payable and accrued liabilities	(2,083)	3,520
Income taxes payable (receivable)	—	(56)
Net cash used in operating activities	(50,732)	(51,152)
Investing Activities		
Acquisition of property and equipment	—	(413)
Acquisition of short-term investments	(90,000)	(35,000)
Maturity of short-term investments	20,000	35,029
Net cash used in investing activities	(70,000)	(384)
Financing activities		
Net proceeds from issuance of common shares in Initial Public Offering	—	85,363
Issuance of common shares on exercise of share options (note 7)	300	44
Net proceeds from issuance of common shares in a public offering (note 7)	24,917	—
Net proceeds from issuance of pre-funded warrants in a public offering (note 7)	23,236	—
Net proceeds from issuance of pre-funded warrants in a private placement (note 7)	24,771	—
Net cash provided by financing activities	73,224	85,407
Net increase (decrease) in cash and cash equivalents during the year	(47,508)	33,871
Cash and cash equivalents – Beginning of year	119,818	85,947
Cash and cash equivalents – End of year	$ 72,310	$ 119,818

The accompanying notes are an integral part of these consolidated financial statements.

Milestone Pharmaceuticals Inc.
Notes to Consolidated Financial Statements
(in thousands of US dollars, except share and per share data)

1 Organization and nature of operations

Milestone Pharmaceuticals Inc. (Milestone or the Company) is a biopharmaceutical company incorporated under the Business Corporations Act of Québec. Milestone is focused on the development and commercialization of innovative cardiovascular medicines. Milestone's lead product candidate, etripamil, is a novel, potent short-acting calcium channel blocker that the Company designed and is developing as a rapid-onset nasal spray to be -administered by patients. The Company is developing etripamil to treat paroxysmal supraventricular tachycardia, atrial fibrillation, and other cardiovascular indications.

2 Summary of significant accounting policies

a) Basis of consolidation

The consolidated financial statements include the accounts of the Company and Milestone Pharmaceuticals USA, Inc. Milestone Pharmaceuticals USA, Inc. began its operations on March 3, 2017. All intercompany transactions and balances have been eliminated.

b) Basis of presentation and use of accounting estimates

These consolidated financial statements of the Company have been presented in United States dollars (USD) and have been prepared in accordance with accounting principles generally accepted in the United States of America (U.S. GAAP), including the applicable rules and regulations of the Securities and Exchange Commission (SEC) regarding financial reporting.

The preparation of consolidated financial statements in conformity with US GAAP requires the Company to make estimates and judgments that affect certain reported amounts of assets and liabilities and disclosure of contingent assets and liabilities at the date of the consolidated financial statements and the reported amounts of revenue and expenses during the period. The Company bases its estimates and assumptions on current facts, historical experience and various other factors that it believes are reasonable under the circumstances, to determine the carrying values of assets and liabilities that are not readily apparent from other sources. Significant estimates and judgments include, but are not limited to, research and development tax credits recoverable, progress of activities performed by the CROs and CMOs which are used to calculate the research and development expense incurred, and share-based compensation. Accordingly, actual results may differ from those estimates and such differences may be material.

The COVID-19 pandemic has had an impact on the Company's business, operations and clinical development timelines. Government orders and restrictions in order to control the spread of the disease have impacted patient recruitment, enrollment and follow-up visits at clinical sites The Company will continue to evaluate the COVID-19 pandemic impact on the development timelines of its clinical programs. Estimates and assumptions about future events and their effects cannot be determined with certainty and therefore require the exercise of judgment. As of the date of issuance of these consolidated financial statements, the Company is not aware of any specific event or circumstance that would require the Company to update its estimates, assumptions and judgments. These estimates may change as new events occur and additional information is obtained and are recognized in the consolidated financial statements as soon as they become known. Actual results could differ from those estimates and any such differences may be material to the Company's consolidated financial statements.

c) Segment information

The Company manages its operations as a single operating segment for the purposes of assessing performance and making operating decisions while focusing on the development and commercialization of innovative cardiovascular medicines.

Milestone Pharmaceuticals Inc.
Notes to Consolidated Financial Statements
(in thousands of US dollars, except share and per share data)

d) Cash and cash equivalents

Cash and cash equivalents consist of cash and highly liquid investments that are readily convertible into cash with original maturities of three months or less at acquisition date.

e) Short term investments

Short term investments are classified as held-to-maturity, are initially recognised at fair value and are subsequently accounted for at amortized cost. They are comprised of guaranteed investment certificates with a maturity greater than 90 days but less than one year and, as such, are classified as current assets.

f) Concentration of credit risk

Financial instruments which potentially subject the Company to concentration of credit risk consist primarily of cash and cash equivalents and investment securities classified as held to maturity. The Company maintains deposits in financial institutions. Management believes that the Company is not exposed to significant credit risk due to the financial position of the depository institutions in which those deposits are held. Additionally, the Company has adopted an investment policy that includes guidelines relative to credit quality, diversification of maturities and liquidity.

g) Currency Risk

The Company is exposed to currency risk due to financial instruments denominated in foreign currencies. The Company is exposed to the Canadian dollar currency risk and does not enter into arrangements to hedge its currency risk exposure.

h) Property and equipment

Property and equipment is stated at historical cost less accumulated amortization. Expenditures for maintenance and repairs are recorded to expense as incurred. The Company reviews its property and equipment whenever events or changes in circumstances indicate that the carrying value of certain assets might not be recoverable and recognizes an impairment loss when it is probable that an asset's realizable value is less than the carrying value. To date, no such impairment losses have been recorded. Amortization is calculated using the straight-line method over the following estimated useful lives of the assets:

Computer hardware and software	3 years
Office equipment	5 years
Furniture and fixtures	5 years
Leasehold improvements	over the lease-term

i) Leases

Effective January 1, 2019, the Company adopted ASC 842, Leases (ASC 842), using the required modified retrospective approach and utilizing the effective date as its date of initial application.

At the inception of an arrangement, the Company determines whether the arrangement is or contains a lease based on the unique facts and circumstances present in the arrangement. Leases with a term greater than one year are recognized on the balance sheet as right-of-use assets and short-term and long-term lease liabilities, as applicable. The Company does not have financing leases.

Operating lease liabilities and their corresponding right-of-use assets are initially recorded based on the present value of lease payments over the expected remaining lease term. Right-out-use assets are subsequently accounted for as long-lived assets, including evaluating for indicators of impairment. Certain adjustments to the right-of-use asset may be required for items such as incentives received. The interest rate implicit in lease contracts is typically not readily

determinable. As a result, the Company utilizes its incremental borrowing rate to discount lease payments, which reflects the fixed rate at which the Company 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. Prospectively, the Company will adjust the right-of-use assets for straight-line rent expense or any incentives received and remeasure the lease liability at the net present value using the same incremental borrowing rate that was in effect as of the lease commencement or transition date.

The Company has elected not to recognize leases with an original term of one year or less on the balance sheet. The Company typically only includes an initial lease term in its assessment of a lease arrangement. Options to renew a lease are not included in the Company's assessment unless there is reasonable certainty that the Company will renew.

j) Pre-funded warrants

Pre-funded warrants allow the holder to pay little or no consideration to receive the shares upon exercise of the warrant. The pre-funded warrants do not meet the definition of a derivative under ASC 815 because their fair value at issuance is equal to the fair value of the shares underlying the warrant. As such, they have the characteristics of a prepaid forward sale of equity. As a result, the pre-funded warrants are accounted for as equity instruments.

k) Share issuance costs

Share issuance costs applicable to the issuance of equity instruments are recorded as a reduction of the financing equity proceeds.

l) Research and development and investment tax credits

Research and development costs are charged to expense as costs are incurred in performing research and development activities. The Company's research and development costs consist primarily of salaries and fees paid to contract research organizations (CROs) and to contract manufacturing organizations (CMOs).

Clinical trial expenses include direct costs associated with CROs, direct CMO costs for the formulation and packaging of clinical trial material, as well as investigator and patient related costs at sites at which the Company's trials are being conducted. Direct costs associated with the Company's CROs and CMOs are generally payable on a time and materials basis, or when milestones are achieved. The invoicing from clinical trial sites can lag several months. The Company records expenses for its clinical trial activities performed by third parties based upon estimates of the percentage of work completed of the total work over the life of the individual study in accordance with agreements established with CROs and clinical trial sites. The Company determines the estimates through discussions with internal clinical personnel, CROs and CMOs as to the progress or stage of completion of trials or services and the agreed upon fee to be paid for such services based on facts and circumstances known to the Company as of each consolidated balance sheet date. The actual costs and timing of clinical trials are highly uncertain, subject of risks and may change depending upon a number of factors, including the Company's clinical development plan. If the actual timing of the performance of services of the level of effort varies from the estimate, the Company will adjust the accrual accordingly.

The Company recognizes the benefit of Canadian research and development tax credits as a reduction of research and development costs for fully refundable investment tax credits and as a reduction of income taxes for investment tax credits that can only be claimed against income taxes payable when there is reasonable assurance that the claim will be recovered.

m) Income taxes

The provision for income taxes is computed using the liability method. Under this method, deferred tax assets and liabilities are determined based on differences between financial reporting and tax bases of assets and liabilities. Deferred tax assets and liabilities are measured using enacted tax rates and laws that will be in effect when the differences are expected to reverse. A valuation allowance is recorded to reduce the carrying amount of deferred income

tax assets when it is more likely than not that these assets will not be realized. Tax benefits related to tax positions not deemed to meet the "more-likely-than-not" threshold are not permitted to be recognized in the consolidated financial statements.

n) Foreign currency translation and transactions

The functional currency of the Company is the US dollar. Accordingly, transactions denominated in currencies other than the functional currency are measured and recorded in the functional currency at the exchange rate in effect on the date of the transactions. At each consolidated balance sheet date, monetary assets and liabilities denominated in currencies other than the functional currency are remeasured using the exchange rate in effect at that date. Non-monetary assets and liabilities and revenue and expense items denominated in foreign currencies are translated into the functional currency using the exchange rate prevailing at the dates of the respective transactions. Any gains or losses arising on remeasurement are included in the consolidated statement of operations.

o) Share based compensation

The Company has a share based compensation plan which is described in detail in note 7 and records all share-based payments, including grants of employee share options, at their fair values. The fair value of share options granted to employees and non-employees is estimated at the date of grant using the Black-Scholes option pricing model. The Company recognizes share based compensation expense over the requisite service period of the individual grants, which equals the vesting period, using the straight-line method. Forfeitures, if any, are recorded as they occur. Any consideration paid by employees on exercising share options and the corresponding portion previously credited to contributed surplus are credited to share capital. The Black-Scholes option pricing model used by the Company to calculate option values was developed to estimate fair value.

The Company approved an employee share purchase plan in April 2019, which became effective on May 8, 2019 and is described in note 7. The plan provides a means by which eligible employees of the company and certain designated companies may be given an opportunity to purchase common shares. The plan permits the company to grant a series of purchase rights to eligible employees under an employee stock purchase plan.

p) Recently adopted accounting pronouncements

New Accounting Policies - Financial Instruments - Credit Losses

In June 2016, the Financial Accounting Standards Board issued Accounting Standards Update 2016-13, Financial Instruments - Credit Losses (Topic 326): Measurement of Credit Losses on Financial Instruments (ASU 2016-13). ASU 2016-13 significantly changes the impairment model for most financial assets and certain other instruments. ASU 2016-13 will require immediate recognition of estimated credit losses expected to occur over the remaining life of many financial assets, which will generally result in earlier recognition of allowances for credit losses on loans and other financial instruments. The Company adopted ASU 2016-13 effective January 1, 2020 and the adoption did not have at the measurement of credit losses.

q) Significant Risks and Uncertainties

The COVID-19 pandemic has had an impact on our business, operations and clinical development timelines. Government orders and restrictions in order to control the spread of the disease have impacted patient recruitment, enrollment and follow-up visits at clinical sites With the global spread of the ongoing COVID-19 pandemic, the Company has implemented business continuity plans designed to address and mitigate the impact of the COVID-19 pandemic on its business. The Company anticipates that the COVID-19 pandemic will continue to have an impact on the development timelines for its clinical programs. The extent to which the COVID-19 pandemic continues to impact its business, its clinical development and regulatory efforts, its corporate development objectives and the value of and market for its common shares will depend on future developments that remain highly uncertain and cannot be predicted

with confidence at this time, such as the ultimate duration of the pandemic, travel restrictions, quarantines, social distancing and business closure requirements in the U.S., Europe and other countries, and the effectiveness of actions taken globally to contain and treat the disease. The global economic slowdown, the overall disruption of global healthcare systems and the other risks and uncertainties associated with the pandemic could have a material adverse effect on the Company's business, financial condition, results of operations and growth prospects.

In addition, the Company is subject to other challenges and risks specific to its business and its ability to execute on its strategy, as well as risks and uncertainties common to companies in the pharmaceutical industry, including, without limitation, risks and uncertainties associated with: obtaining regulatory approval of its product candidate; delays or problems in the supply of its study drug or failure to comply with manufacturing regulations; identifying, acquiring or in-licensing product candidates; pharmaceutical product development and the inherent uncertainty of clinical success; and the challenges of protecting and enhancing its intellectual property rights; and complying with applicable regulatory requirements.

r) Sources of Liquidity and Funding Requirements

Since inception, the Company incurred significant operating losses. Prior to May 2019, the Company financed its operations primarily through sales of convertible preferred shares to accredited investors generating net proceeds of $138.8 million. In May 2019, the Company received net proceeds of $85.4 million from its Initial Public Offering (IPO). In July 2020, the Company received $24.8 million of net proceeds from the private placement of pre-funded warrants to existing shareholders (note 7). In October 2020, the Company concluded an offering of common shares and pre-funded warrants for net proceeds of $48.2 million (note 7).

The Company has incurred operating losses and experienced negative operating cash flows since its inception and anticipates to continue to incur losses for at least the next several years. As of December 31, 2020, the Company had cash, cash equivalents and short-term investments of $142.3 million and an accumulated deficit of $163.5 million.

3 Short-term investments

Short-term investments are comprised of term deposits issued in US currency, earning interest between 0.30% and 0.86%, maturing between January 29, 2021 and August 16, 2021. These short-term investments are in scope of ASC 320, Investments - Debt Securities. The short-term investments maturity is greater than 90 days but less than one year, and they are classified as held to maturity, recorded as current assets and are accounted for at amortized cost.

4 Leases

On June 3, 2019, the Company entered into a new lease arrangement for a three-year term for its office located in Charlotte, NC. The Company recognized the operating lease right-of-use asset and operating lease liabilities at the lease commencement date on September 10, 2019. The interest rate implicit in lease contracts is not readily determinable and the Company does not have a public credit rating and carries no debt. As such, several factors were considered in the determination of the Company's incremental borrowing rate used in determining the present value of lease payments. The Company's examined credit ratings for similar companies, assumed equivalency between the Canadian and U.S. markets for collateralized debt and used rates over the 36-month period. This resulted in an incremental borrowing rate of 8%. Lease expenses are recognized on a straight-line basis over the lease term, which is accomplished by increasing the amortization of the right-of-use asset as interest expense on the lease liability declines over the lease term. The company was not reasonably certain of renewing the lease following the initial term and recognized the right-of-use asset and operating lease liabilities over the 36-month period ending September 30, 2022.

On July 1, 2020, the Company entered into an arrangement for the lease renewal for its headquarters located in Ville Saint-Laurent, Quebec. The 5-year lease term is from December 1, 2020 expiring on November 30, 2025. The Company revalued the operating lease right-of-use asset and operating lease liabilities at the effective lease arrangement date of July 1, 2020. The Company's examined credit ratings for similar companies, assumed equivalency between the

(in thousands of US dollars, except share and per share data)

Canadian and U.S. markets for collateralized debt and used rates for the remaining lease term of 65 months. This resulted in an incremental borrowing rate of 5.26%. Lease expenses are recognized on a straight-line basis over the lease term, which is accomplished by increasing the amortization of the right-of-use asset as interest expense on the lease liability declines over the lease term. The Company is not reasonably certain of renewing the lease following the current renewal option and recognized the right-of-use asset and operating lease liabilities to November 30, 2025.

The Company's two operating office leases right-of-use assets as at December 31 were as follows:

	2020	2019
Opening balance	$ 524	$ 321
New operating lease right-of-use asset	—	401
Right-of-use adjustment renewal on July 1, 2020	735	—
Amortization of right-of-use asset	(279)	(198)
Closing balance	$ 980	$ 524

Operating lease expenses of $318 are included in general and administrative operating expenses in the consolidated statement loss and comprehensive loss, and within operating activities in the statement of cash flows for the year ended December 31, 2020 [2019 - $277], and are comprised of two operating lease right-of-use assets and one operating lease of less than 12 months.

The following table summarizes the future minimum lease payments of right-of-use assets operating lease as at December 31, 2020:

January 1, 2021 to December 31, 2021	$ 293
January 1, 2022 to December 31, 2022	255
January 1, 2023 to December 31, 2023	175
January 1, 2024 to December 31, 2024	175
January 1, 2025 to November 30, 2025	159
	1,057
Less interest	(115)
	$ 942

5 Property and equipment

Property and equipment consist of the following at December 31:

	2020	2019
Computer hardware and software	$ 22	$ 22
Office equipment	406	406
Leasehold improvements	26	26
Total	$ 454	$ 454
Less accumulated depreciation and amortization	(146)	(49)
Property and equipment, net	$ 308	$ 405

During the year ended December 31, 2020 and December 31, 2019, the Company did not record any write off. For the year ended December 31, 2020, amortization expense was $97 [2019-$38] and was included in research and development expense.

Milestone Pharmaceuticals Inc.
Notes to Consolidated Financial Statements
(in thousands of US dollars, except share and per share data)

6 Accounts payable and accrued liabilities

Accounts payable and accrued liabilities comprised the following as of December 31:

	2020	2019
Trade accounts payable	$ 4,641	$ 4,376
Accrued research and development liabilities	152	1,513
Other accrued liabilities	164	331
Accrued compensation and benefits payable	957	1,777
	$ 5,914	$ 7,997

7 Shareholders' equity

Authorized share capital

An unlimited number of common shares, voting and participating, without par value.

In May 2019, the Company completed its initial public offering (IPO). Upon the closing of the IPO, all outstanding redeemable convertible preferred shares of Class A1, A2, B, C, D1 and D2 (collectively known as Convertible Preferred Shares) converted into 17,550,802 common shares.

As of December 31, 2020, 523,821 common shares were available under the Employee Stock Purchase Plans (ESPP) and no common shares have been issued.

During the year ended December 31, 2020, the Company issued a total of 226,352 common shares [2019 - 33,162] for a total cash consideration of $300 [2019 - $44] pursuant to the exercise of stock options at an average exercise price of $1.33 per share [2019 - $1.33]. As a result, an amount of $220 [2019 - $41] previously included in additional paid-in capital related to the exercised options has been credited to share capital and deducted from additional paid-in capital.

Pre-funded warrants – Private Placement

On July 23, 2020, the Company entered into a securities purchase agreement to sell and issue in a private placement pre-funded warrants of 6,655,131 of the Company's common shares, at a purchase price of $3.7465 per pre-funded warrant for aggregate net proceeds of $24.8 million (the Private Placement). The Private Placement closed on July 24, 2020. Each pre-funded warrant is exercisable for one of the Company's common shares at an exercise price of $0.01 per share, has no expiration date, and is immediately exercisable, subject to certain beneficial ownership limitations. The pre-funded warrants are classified and accounted for as equity.

Open Market Sale Agreement

On July 29, 2020, the Company entered into an Open Market Sale Agreement℠ with respect to an at-the-market offering program (ATM Program) under which the Company may issue and sell its common shares having an aggregate offering price of up to $50 million. The Company has not sold shares under the ATM program as of the date of this filing.

Pre-funded warrants and common shares – Public offering

On October 22, 2020, the Company issued (i) 5,095,897 common shares, without par value, at a price to the public of $5.25 per share, and (ii) pre-funded warrants to purchase 4,761,903 common shares at an exercise price equal to $0.01 per share, at a price to the public of $5.24 per common share underlying the pre-funded warrants (the Offering). The net proceeds to the Company from the Offering were $48.2 million. The pre-funded warrants are classified and accounted for as equity.

Milestone Pharmaceuticals Inc.
Notes to Consolidated Financial Statements
(in thousands of US dollars, except share and per share data)

Additional paid-in capital

	2020	2019
Opening balance	$ 3,805	$ 2,655
Share-based compensation expense	4,945	1,191
Exercise of stock options	(220)	(41)
Closing balance	$ 8,530	$ 3,805

Share-based compensation

The Company's board of directors adopted and its shareholders approved the 2019 Equity Incentive Plan (the 2019 Plan) in April 2019, which became effective on May 8, 2019 in connection with the IPO. Initially, the maximum number of the Company's common shares that may be issued under the 2019 Plan was 4,710,564 shares, which is the sum of (1) 1,923,501 new shares, plus (2) the number of shares (not to exceed 2,787,063 shares) (i) that remained available for the issuance of awards under the Company's Stock Option Plan (the "2011 Plan") at the time the 2019 Plan became effective, and (ii) any shares subject to outstanding options or other share awards that were granted under the 2011 Plan that terminate, expire or are otherwise forfeited, reacquired or withheld. In addition, the number of the Company's common shares reserved for issuance under the 2019 Plan will automatically increase on January 1 of each calendar year, starting on January 1, 2020 through January 1, 2029, in an amount equal to 4% of the total number of the Company's capital shares outstanding on the last day of the calendar month before the date of each automatic increase, or a lesser number of shares determined by the Company's board of directors. As of May 8, 2019, the Company's 2011 Plan was terminated and no further option grants will be made under the 2011 Plan.

Under the 2019 Plan and 2011 Plan, unless otherwise decided by the Board of Directors, options vest and are exercisable as follows: 25% vest and are exercisable on the one year anniversary of the grant date and one thirty-sixth ($1/36^{th}$) of the remaining options vest and are exercisable each month thereafter, such that options are vested in full on the four-year anniversary of the grant date. During the year ended December 31, 2020, the Company granted stock options under the 2019 Plan that also vest and are exercisable in equal monthly installments over periods of 12 months to 48 months.

On January 1, 2020, the number of the Company’s common shares reserved for issuance under the 2019 Plan increased by 980,229 common shares. In addition, 72,186 options forfeited under the 2011 Plan after adoption of the 2019 Plan and became available for issuance under the 2019 Plan. As of December 31, 2020, there were 3,369,348 shares available for issuance under the 2019 Plan, of which 1,663,158 shares were available for future grants.

Milestone Pharmaceuticals Inc.
Notes to Consolidated Financial Statements
(in thousands of US dollars, except share and per share data)

The total outstanding and exercisable options from the 2011 Plan and 2019 Plan as at December 31 were as follows:

	2020				2019			
	Number of shares			Weighted average exercise price	Number of shares			Weighted average exercise price
	2019 Plan	2011 Plan	Total		2019 Plan	2011 Plan	Total	
Outstanding at beginning of year - 2011 Plan	—	2,364,526	2,364,526	$ 2.15	—	2,295,045	2,295,045	$ 1.77
Outstanding at beginning of year - 2019 Plan	220,140	—	220,140	20.78	—	—	—	—
Granted - 2011 Plan	—	—	—	—	—	116,742	116,742	9.42
Granted - 2019 Plan	1,534,460	—	1,534,460	12.68	287,138	—	287,138	19.95
Exercised - 2011 Plan	—	(226,352)	(226,352)	1.23	—	(33,162)	(33,162)	1.33
Forfeited - 2011 Plan	—	(58,087)	(58,087)	5.94	—	(14,099)	(14,099)	2.66
Forfeited - 2019 Plan	(45,413)	—	(45,413)	18.53	(66,998)	—	(66,998)	17.22
Cancelled - 2019 Plan	(2,997)	—	(2,997)	21.48	—	—	—	—
Outstanding at end of year	1,706,190	2,080,087	3,786,277	$ 7.29	220,140	2,364,526	2,584,666	$ 3.75
Outstanding at end of year - Weighted average exercise price	$ 13.55	$ 2.15			$ 20.78	$ 2.15		
Exercisable at end of year	268,164	1,536,895	1,805,059	$ 2.94	1,165	1,212,226	1,213,391	$ 1.65
Exercisable at end of year - Weighted average exercise price	$ 8.23	$ 2.02			$ 17.78	$ 1.64		

As of December 31, 2020, the weighted average remaining contractual life was 7.86 years [2019 - 7.8 years] for outstanding options. The weighted average remaining contractual life was 6.91 years for vested options [2019 - 7.0 years]. There were 103,500 options forfeited in 2020 [2019 - 81,097] and there were 2,997 options cancelled in 2020 [2019 - nil]

Options granted are valued using the Black-Scholes option pricing model. Amortization of the fair value of the options over vesting years has been expensed and credited to additional paid-in capital in shareholders' deficit. The weighted average fair values of options granted in 2020 was $8.98 per share [2019 - $11.81]. Share-based compensation expense recognized for the year ended December 31, 2020 was $4,945 [2019 - $1,191].

As of December 31, 2020, there was $13,012 [2019 - $6,464] of total unrecognized compensation cost, related to non-vested share options, which is expected to be recognized over a remaining weighted average vesting period of 2.67 years [2019 - 2.60 years].

	2020				2019			
	Number of options			Weighted average fair value	Number of options			Weighted average fair value
	2019 Plan	2011 Plan	Total		2019 Plan	2011 Plan	Total	
Non-vested share options at beginning of year - 2011 Plan	—	1,152,300	1,152,300	$ 1.88	—	1,706,303	1,706,303	$ 1.35
Non-vested share options at beginning of year - 2019 Plan	218,975	—	218,975	$ 14.44	—	—	—	$ —
Granted - 2011 Plan	—	—	—	—	—	116,742	116,742	6.65
Granted - 2019 Plan	1,534,460	—	1,534,460	8.98	287,138	—	287,138	13.91
Vested, outstanding 2011 Plan	—	(551,026)	(551,026)	1.70	—	(656,646)	(656,646)	1.33
Vested, outstanding 2019 Plan	(269,996)	—	(269,996)	5.80	(1,165)	—	(1,165)	12.16
Forfeited - 2011 Plan	—	(58,082)	(58,082)	4.32	—	(14,099)	(14,099)	1.91
Forfeited - 2019 Plan	(45,413)	—	(45,413)	13.03	(66,998)	—	(66,998)	12.22
Non-vested share options at end of year	1,438,026	543,192	1,981,218	$ 7.96	218,975	1,152,300	1,371,275	$ 3.89
Non-vested share options at end of year - Weighted average fair value	$ 10.28	$ 1.81			$ 14.44	$ 1.88		

Milestone Pharmaceuticals Inc.
Notes to Consolidated Financial Statements
(in thousands of US dollars, except share and per share data)

The following table summarizes information with respect to share options outstanding as of December 31, 2020:

	Options outstanding			Options exercisable		
Exercise price	Number of options	Weighted average remaining contractual life (years)	Weighted average exercise price	Number of options	Weighted average remaining contractual life (years)	Weighted average exercise price
$0.84-$1.00	108,160	2.93	$ 0.90	108,160	2.93	$ 0.90
$1.01-$2.00	1,219,937	6.58	$ 1.47	937,898	6.44	$ 1.44
$2.01-$4.00	1,366,657	8.62	$ 3.22	632,595	8.24	$ 2.99
$4.01-$10.00	147,133	7.67	$ 8.47	55,701	5.27	$ 9.28
$15.01-$20.00	82,380	8.81	$ 17.17	24,768	8.77	$ 17.18
$21.01-$22.45	862,010	9.00	$ 21.65	45,937	8.69	$ 22.45
Total	3,786,277	7.86	$ 7.29	1,805,059	6.91	$ 2.94

The intrinsic value of all outstanding options as of December 31, 2020 was $11.8 million, based on the fair value of our common shares of $6.70 per share at December 31, 2020, of which $7.9 million related to vested options and $3.9 million related to unvested options.

The fair value of share-based payment transaction is measured using Black-Scholes valuation model. This model also requires assumptions, including expected option life, volatility, risk-free interest rate and dividend yield, which greatly affect the calculated values.

The fair value of options granted was estimated using the Black-Scholes option pricing model, resulting in the following weighted average assumptions for the options granted for the years ended December 31, 2020 and 2019:

	2020	2019
Exercise price	$ 12.68	$ 16.90
Share price	$ 12.68	$ 16.90
Volatility	85 %	80 %
Risk-free interest rate	1.03 %	1.92 %
Expected life	5.88 years	6.21 years
Dividend	0 %	0 %

Expected volatility is determined using comparable companies for which the information is publicly available. The risk-free interest rate is determined based on the US sovereign rates benchmark in effect at the time of grant with a remaining term equal to the expected life of the option. Expected option life is determined based on the simplified method as the Company does not have sufficient historical exercise data to provide a reasonable basis upon which to estimate expected term. The simplified method is an average of the contractual term of the options and its ordinary vesting period. Dividend yield is based on the share option’s exercise price and expected annual dividend rate at the time of grant.

No compensation expense is recorded related to an award for which the transfer to the employee is contingent on the attainment of a performance target until it becomes probable that the performance target will be met.

(in thousands of US dollars, except share and per share data)

The Company recognized share-based compensation expense as follows at December 31, 2020 and 2019:

	2020	2019
Administration	$ 2,007	$ 574
Research and development	2,055	495
Commercial activities	883	122
	$ 4,945	$ 1,191

8 Net loss per share

Basic and diluted net loss per common share is determined by dividing net loss applicable to common shareholders by the weighted average number of common shares and pre-funded warrants outstanding during the period. Share-based compensation shares have been excluded from the calculation because their effects would be anti-dilutive. Therefore, the weighted average number of shares used to calculate both basic and diluted loss per share are the same.

The following potentially dilutive securities have been excluded from the computation of diluted weighted average shares outstanding as of December 31, 2020 and 2019, as they would be anti-dilutive:

	2020	2019
Share options	3,786,277	2,584,666

Amounts in the table above reflect the common share equivalents of the noted instruments.

9 Income taxes

A reconciliation between tax expense and the product of accounting income multiplied by the basic income tax rate for the years ended December 31, 2020 and 2019 is as follows:

	2020	2019
Loss before income taxes	$ (49,984)	$ (55,285)
Basic income tax rate	26.33 %	26.30 %
Computed income tax recovery	(13,161)	(14,542)
Effect on income tax rate resulting from		
Accounting charges not deductible for tax purposes	7	23
Non-deductible share-based compensation	1,310	317
Share issue costs	(984)	(2,739)
Tax benefits of current period losses and other tax assets	12,715	16,829
Valuation allowance for prior year adjustment	108	77
Other	(12)	(21)
Income tax expense recovery reported in the consolidated statements of loss and comprehensive loss	$ (17)	$ (56)

The Company has incurred Canadian federal and provincial net operating losses (NOLs) from inception. As of December 31, 2020, the Company has NOL carry-forwards of approximately $123,494 and $122,756, respectively, for Canadian federal and Québec purposes, available to reduce future taxable income, which expire beginning in 2027 through 2040. The Company also has scientific research and experimental development expenditures of approximately $13,735 and $16,247, respectively, for Canadian federal and Québec income tax purposes, which have not been deducted. These expenditures are available to reduce future taxable income and have an unlimited carry-forward period. Research and development tax credits and expenditures are subject to verification by the tax authorities, and, accordingly, these amounts may vary.

The Company has incurred NOLs for U.S. tax purposes. As of December 31, 2020, the Company has carry-forwards of approximately $17,428 related to U.S. NOLs that may be carried forward indefinitely and are available to reduce future taxable income.

Deferred income taxes reflect the net tax effects of temporary differences between the carrying amounts of assets and liabilities for financial reporting purposes and the amounts used for income tax purposes. The net deferred tax assets have not been recognized in these financial statements because the criteria for recognition of these assets were not met.

The Company's deferred tax assets consist of the following for the years ended December 31, 2020 and 2019:

	2020	2019
Net operating loss carry-forwards	36,951	25,965
Tax basis of property and equipment in excess of carrying values	100	103
Federal SR&ED investment tax credits	496	535
Taxation of federal SR&ED investment tax credits	(132)	(142)
Research and development expenditures	3,929	2,686
Financing costs	2,583	2,103
Change in tax rates	25	5
Others	34	11
Total gross deferred tax assets	43,986	31,266
Valuation allowance	(43,986)	(31,266)
Net deferred tax assets	—	—

The Company files income tax returns in Canada and in the United States. The Company is subject to Canada Revenue Agency and Revenu Québec examination for fiscal years 2015 to 2020 due to unexpired statute of limitation periods and is subject to US Federal and state income tax examination for fiscal years 2017 to 2020.

10 Government assistance

The Company incurred research and development expenditures that are eligible for investment tax credits. The investment tax credits recorded are based on management's estimates of amounts expected to be recovered and are subject to audit by the taxation authorities. These amounts (expressed in thousands of US dollars) have been recorded as a reduction of research and development expenditures for an amount of $373 for the year ended December 31, 2020 [2019 - $392].

11 Commitments

In the normal course of business, the Company enters into contracts with clinical research organizations, drug manufacturers and other vendors for preclinical and clinical research studies, research and development supplies and other services and products for operating purposes. These contracts generally provide for termination on notice, and therefore are cancellable contracts. Therefore, as at December 31, 2020 there are no contractual commitments, except for office leases (note 4).

12 Currency risk

The Company is exposed to the financial risk related to the fluctuation of foreign exchange rates and the degree of volatility of those rates. The foreign currency risk is limited to the portion of the Company's business transactions

(in thousands of US dollars, except share and per share data)

denominated in currency other than US dollars. The following table provides an indication of the Company's exposure to the Canadian dollar, which is expressed in US dollars as of December 31:

	2020	2019
Cash	$ 426	$ 149
Accounts payable and accrued liabilities	675	1,680
Net financial position exposure	$ 249	$ 1,531

The Company does not enter into arrangements to hedge its currency risk exposure.

13 Fair value of financial instruments

Pursuant to the accounting guidance for fair value measurement and its subsequent updates, fair value is defined as the price that would be received to sell an asset or paid to transfer a liability (i.e. the exit price) in an orderly transaction between market participants at the measurement date. The accounting guidance establishes a hierarchy for inputs used in measuring fair value that minimizes the use of unobservable inputs by requiring the use of observable market data when available. Observable inputs are inputs that market participants would use in pricing the asset or liability based on active market data. Unobservable inputs are inputs that reflect the assumptions market participants would use in pricing the asset or liability based on the best information available in the circumstances.

The fair value hierarchy is broken down into the three input levels summarized below:

Level 1 — Valuations are based on quoted prices in active markets for identical assets or liabilities and readily accessible by the Company at the reporting date.
Level 2 — Valuations based on inputs other than the quoted prices in active markets that are observable either directly or indirectly in active markets.
Level 3 — Valuations based on unobservable inputs in which there is little or no market data, which requires the Company to develop its own assumptions.

The Company's fair value hierarchy for all its financial assets (by major security type measured at fair value on a recurring basis) for the year ended December 31, 2020, the Company held a Guaranteed investment certificate at Level 1 with a fair value of $70. For the year ended December 31, 2019 is nil, as there was no financial instruments measured at fair value on a recurring basis as of that date.

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

None.

ITEM 9A. CONTROLS AND PROCEDURES.

Evaluation of Disclosure Controls and Procedures

We maintain disclosure controls and procedures, as defined in Rules 13a-15(e) and 15d-15(e) under the Securities Exchange Act of 1934 (the Exchange Act) that are designed to ensure that information required to be disclosed in our periodic and current reports that we file with the SEC is recorded, processed, summarized and reported within the time periods specified in the SEC's rules and forms, and that such information is accumulated and communicated to our management, including our principle executive officer and principle financial officer, as appropriate, to allow timely decisions regarding required disclosure. In designing and evaluating the disclosure controls and procedures, management recognizes that any controls and procedures, no matter how well designed and operated, can provide only reasonable and not absolute assurance of achieving the desired control objectives. In reaching a reasonable level of assurance, management necessarily is required to apply its judgment in evaluating the cost-benefit relationship of possible controls and procedures. In addition, the design of any system of controls also is based in part upon 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, control may become inadequate because of changes in conditions, or the degree of compliance with policies or procedures may deteriorate. Because of the inherent limitations in a cost-effective control system, misstatements due to error or fraud may occur and not be detected.

We carried out an evaluation, under the supervision and with the participation of our management, including our principle executive officer and principle financial officer, of the effectiveness of the design and operation of our disclosure controls and procedures, as defined in Rules 13a-15(e) and 15d-15(e) under the Exchange Act. Based on this evaluation, our principle executive officer and principle financial officer concluded that our disclosure controls and procedures were effective at the reasonable assurance level as of December 31, 2020.

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 Rules 13a-15(f) and 15-d-15(f) of the Exchange Act. Internal control over financial reporting is a process designed under the supervision and with the participation of our management, including our principal executive officer and principal financial officer, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with accounting principles generally accepted in the United States of America.

As of December 31, 2020, management assessed and management concluded the effectiveness of internal control over financial reporting using the criteria set forth by the Committee of Sponsoring Organizations of the Treadway Commission in Internal Control – 2013 Integrated Framework (2013 Framework). Based on this assessment, management concluded that our internal control over financial reporting was effective as of December 31, 2020.

This Annual Report on Form 10-K does not include an attestation report of our independent registered public accounting firm due to a transition period established by the JOBS Act for smaller reporting companies.

Inherent Limitations of Internal Controls

Our management, including our principal executive officer and principal financial officer, does not expect that our disclosure controls and procedures or our internal controls will prevent all errors and all fraud. A control system, no matter how well conceived and operated, can provide only reasonable, not absolute, assurance that the objectives of the control system are met. 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, within the company have been detected. These

inherent limitations include the realities that judgments in decision-making can be faulty, and that breakdowns can occur because of a simple error or mistake. Additionally, controls can be circumvented by the individual acts of some persons, by collusion of two or more people, or by management override of the control. The design of any system of controls also is based in part upon 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 the degree of compliance with the policies or procedures may deteriorate. Because of the inherent limitations in a cost-effective control system, misstatements due to error or fraud may occur and not be detected.

Changes in Internal Control Over Financial Reporting

During the year ended December 31, 2020, there have been no changes in our internal control over financial reporting, as such term is defined in Rules 13a-15(f) and 15d-15(f) promulgated under the Exchange Act, that have materially affected, or are reasonably likely to materially affect, our internal control over financial reporting.

ITEM 9B. OTHER INFORMATION.

None.

PART III

ITEM 10. DIRECTORS, EXECUTIVE OFFICERS AND CORPORATE GOVERNANCE

The information required by this item is incorporated by reference to our Proxy Statement for our 2021 Annual General Meeting of Shareholders to be filed with the SEC within 120 days after the end of the fiscal year ended December 31, 2020.

As part of our system of corporate governance, our board of directors has adopted a code of business conduct and ethics. The code applies to all of our employees, officers (including our principal executive officer, principal financial officer, principal accounting officer or controller, or persons performing similar functions), agents and representatives, including our independent directors and consultants, who are not employees of ours, with regard to their Company-related activities. Our code of business conduct and ethics is available on our website at www.milestonepharma.com. We intend to post on this section of our website any amendment to our code of business conduct and ethics, as well as any waivers of our code of business conduct and ethics, that are required to be disclosed by the rules of the SEC or the Nasdaq Stock Market.

ITEM 11. EXECUTIVE COMPENSATION.

The information required by this item is incorporated by reference to our Proxy Statement for our 2021 Annual Meeting of Shareholders to be filed with the SEC within 120 days after the end of the fiscal year ended December 31, 2020.

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

The information required by this item is incorporated by reference to our Proxy Statement for our 2021 Annual Meeting of Shareholders to be filed with the SEC within 120 days after the end of the fiscal year ended December 31, 2020.

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

The information required by this item is incorporated by reference to our Proxy Statement for our 2021 Annual General Meeting of Shareholders to be filed with the SEC within 120 days after the end of the fiscal year ended December 31, 2020.

ITEM 14. PRINCIPAL ACCOUNTING FEES AND SERVICES.

The information required by this item is incorporated by reference to our Proxy Statement for our 2021 Annual General Meeting of Shareholders to be filed with the SEC within 120 days after the end of the fiscal year ended December 31, 2020.

PART IV

ITEM 15. EXHIBITS, FINANCIAL STATEMENT SCHEDULES.

(a)(1) Financial Statements

See Index to Consolidated Financial Statements on page 103 of this Annual Report on Form 10-K, which is incorporated into this item by reference.

(a)(2) Financial Statement Schedules

All financial statement schedules are omitted because they are not applicable or the required information is shown in the financial statements or notes thereto.

(b) Exhibits

The following list of exhibits includes exhibits submitted with this Annual Report on Form 10-K as filed with the SEC and others incorporated by reference to other filings.

EXHIBIT NUMBER	DESCRIPTION
3.1	Amended Articles of Incorporation (incorporated herein by reference to Exhibit 3.1 to the Registrant's Current Report on Form 8-K (File No. 001-38899), filed with the SEC on May 15, 2019).
3.2	Amended and Restated Bylaws (incorporated herein by reference to Exhibit 3.2 to the Registrant's Current Report on Form 8-K (File No. 001-38899), filed with the SEC on May 15, 2019).
4.1	Form of Common Share Certificate (incorporated herein by reference to Exhibit 4.1 to Amendment No. 1 to the Registrant's Registration Statement on Form S-1 (File No. 333-230846), filed with the SEC on April 29, 2019).
4.2	Form of Pre-Funded Warrant to Purchase Common Shares (incorporated herein by reference to Exhibit 4.1 to the Registrant's Current Report on Form 8-K (File No. 001-38899), filed with the SEC on July 23, 2020.
4.3	Form of Pre-Funded Warrant (incorporated herein by reference to Exhibit 4.1 to the Registrant's Current Report on Form 8-K (File No. 001-38899), filed with the SEC on October 26, 2020.
4.4	Third Amended and Restated Registration Rights Agreement, by and among the Company and certain of its shareholders, dated October 15, 2018 (incorporated herein by reference to Exhibit 4.2 to the Registrant's Registration Statement on Form S-1 (File No. 333-230846), filed with the SEC on April 12, 2019).
4.5	Description of Securities Registered pursuant to Section 12 of the Securities Exchange Act of 1934, as amended
10.1+	Third Amended and Restated Stock Option Plan (incorporated herein by reference to Exhibit 10.1 to the Registrant's Registration Statement on Form S-1 (File No. 333-230846), filed with the SEC on April 12, 2019).
10.2+	Form of Award and Grant Notices under the Third Amended and Restated Stock Option Plan (incorporated herein by reference to Exhibit 10.2 to the Registrant's Registration Statement on Form S-1 (File No. 333-230846), filed with the SEC on April 12, 2019).
10.3+	2019 Equity Incentive Plan (incorporated herein by reference to Exhibit 4.8 to the Registrant's Registration Statement on Form S-8 (File No. 333-231347), filed with the SEC on May 9, 2019).
10.4+	Form of U.S. Stock Option Grant Notice and Stock Option Agreement under the 2019 Equity Incentive Plan (incorporated herein by reference to Exhibit 10.4 to Amendment No. 1 to the Registrant's Registration Statement on Form S-1 (File No. 333-230846), filed with the SEC on April 29, 2019).
10.5+	Form of U.S. Restricted Stock Unit Grant Notice and Restricted Stock Unit Award Agreement under the 2019 Equity Incentive Plan (incorporated herein by reference to Exhibit 10.5 to Amendment No. 1 to the Registrant's Registration Statement on Form S-1 (File No. 333-230846), filed with the SEC on April 29, 2019).
10.6+	Form of Canadian Stock Option Grant Notice and Option Agreement under the 2019 Equity Incentive Plan (incorporated herein by reference to Exhibit 10.6 to Amendment No. 1 to the Registrant's Registration Statement on Form S-1 (File No. 333-230846), filed with the SEC on April 29, 2019).

10.7+	Form of Canadian Restricted Stock Unit Grant Notice and Restricted Stock Unit Award Agreement under the 2019 Equity Incentive Plan (incorporated herein by reference to Exhibit 10.7 to Amendment No. 1 to the Registrant's Registration Statement on Form S-1 (File No. 333-230846), filed with the SEC on April 29, 2019).
10.8+	2019 Employee Share Purchase Plan (incorporated herein by reference to Exhibit 4.13 to the Registrant's Registration Statement on Form S-8 (File No. 333-231347), filed with the SEC on May 9, 2019).
10.9+	Amended and Restated Employment Agreement between Joseph Oliveto and Milestone Pharmaceuticals USA, Inc. (incorporated herein by reference to Exhibit 10.9 to Amendment No. 1 to the Registrant's Registration Statement on Form S-1 (File No. 333-230846), filed with the SEC on April 29, 2019), as amended by First Amendment to Amended and Restated Employment Agreement between Joseph Oliveto and Milestone Pharmaceuticals USA, Inc. (incorporated herein by reference to Exhibit 10.1 to Registrant's Current Report on Form 8-K (File No. 001-38899), filed with the SEC on June 8, 2020).
10.10+	Employment Agreement between Amit Hasija and Milestone Pharmaceuticals USA, Inc. (incorporated herein by reference to Exhibit 10.1 to the Registrant's Current Report on Form 8-K (File No. 001-38899), filed with the SEC on September 9, 2019), as amended by First Amendment to Employment Agreement between Amit Hasija and Milestone Pharmaceuticals USA, Inc. (incorporated herein by reference to Exhibit 10.2 to Registrant's Current Report on Form 8-K (File No. 001-38899), filed with the SEC on June 8, 2020).
10.11+	Amended and Restated Employment Agreement between Francis Plat and Milestone Pharmaceuticals Inc. (incorporated herein by reference to Exhibit 10.11 to Amendment No. 1 to the Registrant's Registration Statement on Form S-1 (File No. 333-230846), filed with the SEC on April 29, 2019), as amended by Amending Agreement between Francis Plat and Milestone Pharmaceuticals Inc. (incorporated herein by reference to Exhibit 10.3 to the Registrant's Current Report on Form 8-K (File No. 001-38899), filed with the SEC on June 8, 2020).
10.12+	Securities Purchase Agreement dated July 22, 2020 (incorporated herein by reference to Exhibit 10.1 to the Registrant's Current Report on Form 8-K (File No. 001-38899), filed with the SEC on July 23, 2020).
10.13+	Open Market Sale Agreement℠, dated July 29, 2020, by and between Milestone Pharmaceuticals Inc. and Jefferies LLC 2020 (incorporated herein by reference to Exhibit 10.1 to the Registrant's Current Report on Form 8-K (File No. 001-38899), filed with the SEC on July 29, 2020).
10.14+	Form of Indemnity Agreement (incorporated herein by reference to Exhibit 10.14 to the Registrant's Registration Statement on Form S-1 (File No. 333-230846), filed with the SEC on April 12, 2019).
10.15+	Amended and Restated Employment Agreement between Lorenz Muller and Milestone Pharmaceuticals USA, Inc. (incorporated herein by reference to Exhibit 10.12 to Amendment No. 1 to the Registrant's Registration Statement on Form S-1 (File No. 333-230846), filed with the SEC on April 29, 2019).
23.1	Consent of PricewaterhouseCoopers LLP, an Independent Registered Public Accounting Firm.
24.1	Power of Attorney (included on the signature page to this registration statement).
31.1	Certification of Principal Executive Officer pursuant to Rules 13a-14(a) and 15d-14(a) promulgated under the Securities Exchange Act of 1934, as adopted pursuant to Section 302 of the Sarbanes-Oxley Act of 2002
31.2	Certification of Principal Financial Officer pursuant to Rules 13a-14(a) and 15d-14(a) promulgated under the Securities Exchange Act of 1934, as adopted pursuant to section 302 of the Sarbanes-Oxley Act of 2002
32.1^	Certification of Principal Executive Officer and Principal Financial Officer pursuant to Rules 13a-14(b) and 15d-14(b) promulgated under the Securities Exchange Act of 1934 and 18 U.S.C. Section 1350, as adopted pursuant to section 906 of The Sarbanes-Oxley Act of 2002
101.INS	XBRL Instance Document
101.SCH	XBRL Taxonomy Extension Schema Document
101.CAL	XBRL Taxonomy Extension Calculation Linkbase Document
101.DEF	XBRL Taxonomy Extension Definition Linkbase Document
101.LAB	XBRL Taxonomy Extension Label Linkbase Document
101.PRE	XBRL Taxonomy Extension Presentation Linkbase Document

+ Indicates a management contract or compensatory plan

^ These certifications are being furnished solely to accompany this Annual Report pursuant to 18 U.S.C. Section 1350, and are not being filed for purposes of Section 18 of the Securities Exchange Act of 1934, as amended, and are not to be incorporated by reference into any filing of the Registrant, whether made before or after the date hereof, regardless of any general incorporation language in such filing.

ITEM 16. FORM 10-K SUMMARY

Not applicable

SIGNATURES

Pursuant to the requirements of Section 13 or 15(d) of the Securities Exchange Act of 1934, the Company has duly caused this report to be signed on its behalf by the undersigned, thereunto duly authorized.

Milestone Pharmaceuticals Inc.

Dated: March 29, 2021

/s/ Joseph Oliveto
Joseph Oliveto
Chief Executive Officer

POWER OF ATTORNEY

KNOW ALL BY THESE PRESENTS, that each person whose signature appears below constitutes and appoints Joseph Oliveto and Amit Hasija, and each of them, as his or her true and lawful attorneys-in-fact and agents, each with the full power of substitution, for him or her and in his or her name, place or stead, in any and all capacities, to sign any and all amendments to this report, with exhibits thereto and other documents in connection therewith, with the Securities and Exchange Commission, granting unto said attorneys-in-fact and agents, and each of them, full power and authority to do and perform each and every act and thing requisite and necessary to be done in and about the premises, as fully to all intents and purposes as he or she might or could do in person, hereby ratifying and confirming all that said attorneys-in-fact and agents, or their, his substitute or substitutes, may lawfully do or cause to be done by virtue hereof.

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 Company and in the capacities indicated on the 29th of March 2021.

/s/ Joseph Oliveto Joseph Oliveto	Chief Executive Officer (principal executive officer)
/s/ Amit Hasija Amit Hasija	Chief Financial Officer (principal financial officer and principle accounting officer)
/s/ Robert J. Wills Robert Wills	Chairman of the Board
/s/ Michael Tomsicek Michael Tomsicek	Director
/s/ Paul Truex Paul Truex	Director
/s/ Debra K. Liebert Debra K. Liebert	Director
/s/ Richard Pasternak Richard Pasternak	Director
/s/ Lisa M. Giles Lisa M. Giles	Director

DESCRIPTION OF THE REGISTRANT'S SECURITIES REGISTERED PURSUANT TO SECTION 12 OF THE SECURITIES EXCHANGE ACT OF 1934

The following description sets forth certain material terms and provisions of the securities of Milestone Pharmaceuticals Inc. (the "Company") that are registered under Section 12 of the Securities Exchange Act of 1934, as amended. The following description of our securities is intended as a summary only and is qualified in its entirety by reference to our articles of incorporation and amendments thereto and our bylaws, each of which are filed as exhibits to the Annual Report on Form 10-K of which this description is a part, and to the applicable provisions of the Business Corporations Act (Québec) (BCA).

General

Based upon shares outstanding as of December 31, 2020, our share capital consists of an unlimited number of common shares, no par value per share, and an unlimited number of preferred shares, no par value per share, none of which are issued and outstanding.

Common Shares

Voting Rights

Under our articles of incorporation, the holders of common shares are entitled to one vote for each share held at any meeting of the shareholders.

Dividends

Subject to the prior rights of holders of our preferred shares, if applicable, the holders of common shares are entitled to receive dividends as and when declared by our board of directors. We have never declared or paid cash dividends on our share capital, and we do not currently intend to pay any cash dividends on our share capital in the foreseeable future. We currently intend to retain all available funds and any future earnings, if any, to fund the development and expansion of our business. Any future determination related to dividend policy will be made at the discretion of our board of directors, subject to applicable laws, and will depend upon, among other factors, our results of operations, financial condition, contractual restrictions and capital requirements. In addition, our ability to pay cash dividends on our share capital in the future may be limited by the terms of any future debt or preferred securities we issue or any credit facilities we enter into.

Liquidation

Subject to the prior payment to holders of our preferred shares, if any, in the event of our liquidation, dissolution or winding-up or other distribution of our assets among our shareholders, the holders of common shares are entitled to share *pro rata* in the distribution of the balance of our assets.

Rights and Preferences

The holders of common shares have no preemptive, conversion rights or other subscription rights. There are no redemption or sinking fund provisions applicable to our common shares. There is no provision in our articles of incorporation requiring the holders of common shares to contribute additional capital or permitting or restricting the issuance of additional securities or any other material restrictions. The rights, preferences and privileges of the holders of common shares may be subject to, and adversely affected by, the rights of the holders of any series of preferred shares that we may designate in the future.

Preferred Shares

We do not have any preferred shares outstanding. Under our articles of incorporation, we are authorized to issue, without shareholder approval, an unlimited number of preferred shares, issuable in one or more series, and, subject to the provisions of the BCA, having such designations, rights, privileges, restrictions and conditions, including dividend and voting rights, as our board of directors may determine, and such rights and privileges, including dividend and voting rights, may be superior to those of the common shares. The issuance of preferred shares, while providing flexibility in connection with possible acquisitions and other corporate purposes, could, among other things, have the effect of delaying, deferring or preventing a change in control of our company and might adversely affect the market price of our common shares and the voting and other rights of the holders of common shares. We have no current plans to issue any preferred shares.

Registration Rights

Holders of certain of the common shares issued upon the conversion of our preferred shares in connection with our initial public offering on May 13, 2019 are entitled to certain rights with respect to registration of any securities held by such investors, as well as any under the Securities Act. These shares are referred to as registrable securities. The holders of these registrable securities possess registration rights pursuant to the terms of our third amended and restated registration rights agreement and are described below. The registration of common shares pursuant to the exercise of the registration rights described below would enable the holders to trade these shares without restriction under the Securities Act when the applicable registration statement is declared effective. We will pay the registration expenses, other than underwriting discounts, selling commissions and share transfer taxes for the shares registered pursuant to the demand, piggyback and Form S-3 registrations described below. Expenses relating to underwriting discounts, selling commissions and share transfer taxes for the shares registered will be borne by us and the participating holders in proportion to the number of common shares sold by each, or, as between the participating holders, as such participating holders may otherwise agree.

Generally, in an underwritten offering, the managing underwriter, if any, has the right, subject to specified conditions, to limit the number of shares the holders may include. The demand, piggyback and Form S-3 registration rights described below will expire upon the earliest of (i) the occurrence of certain mergers or consolidations of the company, (ii) the date on which the shares that are the subject to the agreement are publicly sold, or if they may be publicly sold: (x) pursuant to Rule 144 of the Securities Act and (y) Section 2.5 of Regulation 45-102 respecting Resale of Securities, as adopted by the Canadian Securities Administrators, and (iii) five years after the completion of our initial public offering.

Demand Registration Rights

Beginning on May 13, 2020, the one year anniversary of the closing of our initial public offering, certain holders of the common shares issued upon conversion of our preferred shares will be entitled to certain demand registration rights. These demand rights permit holders of at least 25% of the registrable securities then outstanding, on not more than two occasions, to request that we register all or a portion of their shares, subject to certain specified exceptions, pursuant to either the Securities Act, Regulation 41-101 respecting General Prospectus Requirements, as adopted by Canadian Securities Administrators or both.

Piggyback Registration Rights

Holders of certain of the common shares issued upon conversion of our preferred shares are entitled to include their shares of registrable securities in any registration statement we file in the event that we propose to register any of our securities under the Securities Act in an offering, either for our own account or for the account of other security holders, subject to specified conditions and limitations.

S-3 Registration Rights

Holders of certain of the common shares issued upon conversion of our preferred shares are entitled to certain Form S-3 registration rights. The holders of at least 25% of the registrable securities then outstanding may, on not more than two occasions within any 12-month period, request that we register all or a portion of their shares on Form S-3 or a form under the Canada-United States Multijurisdictional Disclosure System, or the MJDS, if we are qualified to file a registration statement on Form S-3 or the MJDS, as applicable, subject to specified exceptions. Such request for registration on Form S-3 must cover securities with an aggregate offering price which equals or exceeds$10.0 million. The right to have such shares registered on Form S-3 is further subject to other specified conditions and limitations.

Indemnification

The third amended and restated registration rights agreement contains customary cross-indemnification provisions, pursuant to which we are obligated to indemnify the selling shareholders in the event of material misstatements or omissions in the registration statement attributable to us, and they are obligated to indemnify us for material misstatements or omissions in the registration statement attributable to them.

Transfer Agent and Registrar

Our transfer agent and registrar for our common shares is Computershare Investor Services Inc., with an address of 1500 Robert-Bourassa Boulevard, 7th Floor, Montréal, Quebec H3A 3S8.

Nasdaq Global Market Listing

Our common shares are listed on The Nasdaq Global Market under the trading symbol "MIST."

Advance Notice Procedures and Shareholder Proposals

Under the BCA, shareholders may make proposals for matters to be considered at the annual general meeting of shareholders. Such proposals must be sent to us in advance of any proposed meeting by delivering a timely written notice in proper form to our registered office in accordance with the requirements of the BCA. The notice must include information on the business the shareholder intends to bring before the meeting.

In addition, our bylaws require that shareholders provide us with advance notice of their intention to nominate any persons, other than those nominated by management, for election to our board of directors at a meeting of shareholders.

These provisions could have the effect of delaying the nomination of certain persons for director that are favored by the holders of a majority of our outstanding voting securities.

Exhibit 23.1

CONSENT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

We hereby consent to the incorporation by reference in the Registration Statements on Form S-8 (Nos. 333-231347 and 333-236971) of Milestone Pharmaceuticals Inc. of our report dated March 29, 2021 relating to the consolidated financial statements, which appears in this Form 10-K.

/s/ PricewaterhouseCoopers LLP
Montréal, Québec, Canada

March 29, 2021

Exhibit 31.1

CERTIFICATION PURSUANT TO
RULES 13a-14(a) AND 15d-14(a) UNDER THE SECURITIES EXCHANGE ACT OF 1934,
AS ADOPTED PURSUANT TO SECTION 302 OF THE SARBANES-OXLEY ACT OF 2002

I, Joseph Oliveto, certify that:

1. I have reviewed this Annual Report on Form 10-K of Milestone Pharmaceuticals 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 officer(s) 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 officer(s) 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 functions):

   (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 29, 2021

/s/ Joseph Oliveto
Joseph Oliveto
President and Chief Executive Officer
(Principal Executive Officer)

Exhibit 31.2

CERTIFICATION PURSUANT TO
RULES 13a-14(a) AND 15d-14(a) UNDER THE SECURITIES EXCHANGE ACT OF 1934,
AS ADOPTED PURSUANT TO SECTION 302 OF THE SARBANES-OXLEY ACT OF 2002

I, Amit Hasija, certify that:

1. I have reviewed this Annual Report on Form 10-K of Milestone Pharmaceuticals 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 officer(s) 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 officer(s) 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 functions):

   (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 29, 2021

/s/ Amit Hasija
Amit Hasija
Chief Financial Officer
(Principal Financial and Accounting 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

Pursuant to the requirement set forth in Rule 13a-14(b) of the Securities Exchange Act of 1934, as amended, (the "Exchange Act") and Section 1350 of Chapter 63 of Title 18 of the United States Code (18 U.S.C. §1350), Joseph Oliveto, Chief Executive Officer of Milestone Pharmaceuticals Inc. (the "Company"), and Amit Hasija, Chief Financial Officer of the Company, each hereby certifies that, to the best of his or her knowledge:

1. The Company's Annual Report on Form 10-K for the period ended December 31, 2020, to which this Certification is attached as Exhibit 32.1 (the "Periodic Report"), fully complies with the requirements of Section 13(a) or Section 15(d) of the Exchange Act; and

2. The information contained in the Periodic Report fairly presents, in all material respects, the financial condition and results of operations of the Company.

Dated: March 29, 2021

/s/ Joseph Oliveto	/s/ Amit Hasija
Joseph Oliveto	Amit Hasija
Chief Executive Officer	Chief Financial Officer
(Principal Executive Officer)	(Principal Financial and Accounting Officer)