

**UNITED STATES
SECURITIES AND EXCHANGE COMMISSION**

Washington, D.C. 20549

AMENDMENT NO. 1

TO

FORM S-3

REGISTRATION STATEMENT
UNDER

THE SECURITIES ACT OF 1933

Milestone Pharmaceuticals Inc.

(Exact name of registrant as specified in its charter)

Québec
(State or other jurisdiction of
incorporation or organization)

Not applicable
(I.R.S. Employer
Identification Number)

**1111 Dr. Frederik-Philips Boulevard, Suite 420
Montréal, Québec CA H4M 2X6
(514) 336-0444**

(Address, including zip code, and telephone number, including area code, of registrant's principal executive offices)

**Joseph Oliveto
Chief Executive Officer
Milestone Pharmaceuticals USA Inc.
7422 Carmel Executive Park Drive
Suite 300
Charlotte, NC 28226
(514) 336-0444**

(Name, address, including zip code, and telephone number, including area code, of agent for service)

Copies to:

**Ryan S. Sansom
Marc Recht
Divakar Gupta
Cooley LLP
500 Boylston Street, 14th Floor
Boston, MA 02116
(617) 937-2300**

**Nathalie Beauregard
Francois Paradis
Osler, Hoskin & Harcourt LLP
1000 De La Gauchetière Street West,
Suite 2100
Montréal, Québec CA H3B 4W5
(514) 904-8100**

Approximate date of commencement of proposed sale to the public: From time to time after the effective date of this Registration Statement.

If the only securities being registered on this Form are being offered pursuant to dividend or interest reinvestment plans, please check the following box:

If any of the securities being registered on this Form are to be offered on a delayed or continuous basis pursuant to Rule 415 under the Securities Act of 1933, as amended, other than securities offered only in connection with dividend or interest reinvestment plans, check the following box:

If this Form is filed to register additional securities for an offering pursuant to Rule 462(b) under the Securities Act, please check the following box and list the Securities Act registration statement number of the earlier effective registration statement for the same offering:

If this Form is a post-effective amendment filed pursuant to Rule 462(c) under the Securities Act, check the following box and list the Securities Act registration statement number of the earlier effective registration statement for the same offering.

If this Form is a registration statement pursuant to General Instruction I.D. or a post-effective amendment thereto that shall become effective upon filing with the Commission pursuant to Rule 462(e) under the Securities Act, check the following box.

If this Form is a post-effective amendment to a registration statement filed pursuant to General Instruction I.D. filed to register additional securities or additional classes of securities pursuant to Rule 413(b) under the Securities Act, check the following box.

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 7(a)(2)(B) of the Securities Act.

CALCULATION OF REGISTRATION FEE

Title of each class of securities to be registered	Amount to be registered ⁽¹⁾	Proposed maximum offering price per unit ⁽²⁾	Proposed maximum aggregate offering price ⁽²⁾	Amount of registration fee
Common Shares, no par value per share	910,746	\$5.66	\$ 5,154,822.36	\$477.85

(1) There are being registered hereunder 910,746 of our common shares issuable upon the exercise of pre-funded warrants with an exercise price of \$0.01 per share held by the selling shareholders named in this registration statement. Pursuant to Rule 416 under the Securities Act of 1933, as amended, this registration statement also covers such additional number of our common shares as may be issuable from time to time upon exercise of such pre-funded warrants as a result of share splits, share dividends, capitalizations or similar events.

(2) Estimated solely for the purposes of calculating the registration fee. Pursuant to Rule 457(c) under the Securities Act, the registration fee has been calculated based upon the average of the high and low prices, as reported by The Nasdaq Global Market, for our common shares on October 28, 2021.

The Registrant hereby amends this Registration Statement on such date or dates as may be necessary to delay its effective date until the Registrant shall file a further amendment that specifically states that this Registration Statement shall thereafter become effective in accordance with Section 8(a) of the Securities Act of 1933, as amended, or until the Registration Statement shall become effective on such date as the Securities and Exchange Commission, acting pursuant to said Section 8(a), may determine.

SUBJECT TO COMPLETION, DATED OCTOBER 28, 2021

PROSPECTUS

910,746 Common Shares



This prospectus covers the offer and resale by the selling shareholders identified in this prospectus of up to an aggregate of 910,746 of our common shares, no par value per share, issuable upon exercise of pre-funded warrants sold to the selling shareholders in a private placement on May 21, 2021. We refer to these underlying common shares as the warrant shares.

We are not selling any common shares under this prospectus and will not receive any proceeds from the sale by the selling shareholders of the warrant shares. We will, however, receive the nominal exercise price per share of \$0.01 for any pre-funded warrants exercised for cash.

Sales of the warrant shares by the selling shareholders may occur at fixed prices, at market prices prevailing at the time of sale, at prices related to prevailing market prices or at negotiated prices. The selling shareholders may sell warrant shares to or through underwriters, broker-dealers or agents, who may receive compensation in the form of discounts, concessions or commissions from the selling shareholders, the purchasers of the warrant shares, or both.

We are paying the cost of registering the warrant shares covered by this prospectus as well as various related expenses. The selling shareholders are responsible for all selling commissions, transfer taxes and other costs related to the offer and sale of their warrant shares.

Our common shares are listed for trading on The Nasdaq Global Select Market under the symbol "MIST." On October 28, 2021, the last reported sale price of our common shares was \$5.66 per share.

Investing in our common shares involves a high degree of risk. You should review carefully the risks and uncertainties described in the section titled "Risk Factors" on page 2 of this prospectus and any similar section contained in the applicable prospectus supplement and in any free writing prospectuses we have authorized for use in connection with a specific offering, and under similar headings in the documents that are incorporated by reference into this prospectus.

Neither the Securities and Exchange Commission nor any state securities commission has approved or disapproved of these securities or determined if this prospectus is truthful or complete. Any representation to the contrary is a criminal offense.

The information in this preliminary prospectus is not complete and may be changed. We may not sell these securities or accept an offer to buy these securities until the registration statement filed with the Securities and Exchange Commission is effective. This prospectus is not an offer to sell these securities and it is not soliciting offers to buy these securities in any state where such offer or sale is not permitted.

The date of this prospectus is _____, 2021.

TABLE OF CONTENTS

<u>ABOUT THIS PROSPECTUS</u>	<u>i</u>
<u>PROSPECTUS SUMMARY</u>	<u>1</u>
<u>RISK FACTORS</u>	<u>2</u>
<u>SPECIAL NOTE REGARDING FORWARD-LOOKING STATEMENTS</u>	<u>3</u>
<u>USE OF PROCEEDS</u>	<u>5</u>
<u>SELLING SHAREHOLDERS</u>	<u>6</u>
<u>PLAN OF DISTRIBUTION</u>	<u>8</u>
<u>LEGAL MATTERS</u>	<u>10</u>
<u>EXPERTS</u>	<u>10</u>
<u>WHERE YOU CAN FIND ADDITIONAL INFORMATION</u>	<u>10</u>
<u>INCORPORATION OF CERTAIN INFORMATION BY REFERENCE</u>	<u>11</u>

ABOUT THIS PROSPECTUS

This prospectus is part of a registration statement on Form S-3 that we filed with the Securities and Exchange Commission, or the SEC, using a “shelf” registration process. Under this shelf process, certain selling shareholders may from time to time sell the common shares described in this prospectus in one or more offerings or otherwise as described under “Plan of Distribution.”

This prospectus may be supplemented from time to time by one or more prospectus supplements. Such prospectus supplements may also add, update or change information contained in this prospectus. If there is any inconsistency between the information in this prospectus and the applicable prospectus supplement, you must rely on the information in the prospectus supplement. You should carefully read both this prospectus and any applicable prospectus supplement together with additional information described under the heading “Where You Can Find More Information” before deciding to invest in any shares being offered.

Neither we nor the selling shareholders have authorized anyone to provide any information other than that contained or incorporated by reference in this prospectus or in any related prospectus supplement or any free writing prospectus that we have authorized. We take no responsibility for, and can provide no assurance as to the reliability of, any other information that others may give you. The shares are not being offered in any jurisdiction where the offer is not permitted. You should not assume that the information contained in or incorporated by reference in this prospectus is accurate as of any date other than the respective dates of such document. Our business, financial condition, results of operations and prospects may have changed since those dates.

Unless otherwise mentioned or unless the context requires otherwise, all references in this prospectus to “Milestone,” “company,” “we,” “us” and “our” or similar references refer to Milestone Pharmaceuticals Inc. and its consolidated subsidiary.

SUMMARY

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 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.

Corporate Background

We were incorporated under the Canada Business Corporations Act in 2003 and continued under the Business Corporations Act (Québec) in 2017. 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. In January 2017, we incorporated our wholly owned subsidiary, Milestone Pharmaceuticals USA, Inc., a Delaware corporation. Our corporate website address is www.milestonepharma.com. Information contained on, or accessible through, our website is not a part of this prospectus. We have included our website in this prospectus solely as an inactive textual reference.

Implications of Being an Emerging Growth Company and Smaller Reporting Company

We qualify as an “emerging growth company” as defined in the Jumpstart Our Business Startups Act of 2012, or the JOBS Act. An emerging growth company may take advantage of relief from some of the reporting requirements and other burdens that are otherwise applicable generally to public companies. These provisions include:

- being permitted to provide only two years of audited financial statements, in addition to any required unaudited interim financial statements, with correspondingly reduced “Management’s Discussion and Analysis of Financial Condition and Results of Operations” disclosure;
- 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 in our periodic reports, proxy statements and registration statements; and
- not being required to hold a nonbinding advisory vote on executive compensation and shareholder approval of any golden parachute payments not previously approved.

RISK FACTORS

Investing in our common shares involves a high degree of risk. Before deciding whether to invest in our common shares, you should consider carefully the risks and uncertainties described below and under the section titled Risk Factors contained in our most recent Annual Report on Form 10-K, as well as any amendments thereto reflected in subsequent filings with the SEC, which are incorporated by reference into this prospectus in their entirety, together with other information in this prospectus, the documents incorporated by reference herein, any prospectus supplement and any free writing prospectus that we may authorize. If any of the risks described in our most recent Annual Report on Form 10-K, the other filings incorporated by reference herein or in any prospectus supplement or any free writing prospectus that we may authorize occurs, our business, financial condition, results of operations and future growth prospects could be harmed. In these circumstances, the market price of our common shares could decline, and you may lose all or part of your investment. For more information, see the sections entitled “Where You Can Find Additional Information” and “Special Note Regarding Forward-Looking Statements.”

SPECIAL NOTE REGARDING FORWARD-LOOKING STATEMENTS

This prospectus and the documents incorporated by reference herein and any free writing prospectus that we have authorized for use in connection with this offering contain forward-looking statements within the meaning of Section 27A of the Securities Act of 1933, as amended, or the Securities Act, and Section 21E of the Securities Exchange Act of 1934, or the Exchange Act. These statements are based on our management's current beliefs, expectations and assumptions about future events, conditions and results and on information currently available to us. Discussions containing these forward-looking statements may be found, among other places, in the Sections entitled "Business," "Risk Factors" and "Management's Discussion and Analysis of Financial Condition and Results of Operations" incorporated by reference from our most recent Annual Report on Form 10-K and our most recent Quarterly Report on Form 10-Q, as well as any amendments thereto, filed with the SEC.

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" or the negative or plural of those terms, and similar expressions intended to identify statements about the future, although not all forward-looking statements contain these words. These forward-looking statements involve known and unknown risks, uncertainties and other factors that may cause our actual results, levels of activity, performance or achievements to be materially different from the information expressed or implied by these statements.

Any statements in this prospectus, the documents incorporated by reference herein, or in any free writing prospectus that we have authorized for us in connection with this offering about our expectations, beliefs, plans, objectives, assumptions or future events or performance are not historical facts and are forward-looking statements. Forward-looking statements may include, but are not limited to, statements regarding:

- 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 with 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;
- the results of our collaborations or obtain additional funding, including our license agreement with Ji Xing Pharmaceuticals Limited to develop and, if approved by regulatory authorities, commercialize etripamil in China and Taiwan;
- our ability to establish additional 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 payer 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
- other factors that may impact our financial results.

These forward-looking statements are subject to a number of risks and uncertainties. We discuss in greater detail many of these risks in our most recent Annual Report on Form 10-K, as well as any amendments thereto reflected in subsequent filings with the SEC, which are incorporated by reference into this prospectus in their entirety. You should refer to the “Risk Factors” section contained in the documents incorporated by reference herein, and applicable prospectus supplement and any free writing prospectus that we have authorized for use in connection with this offering 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. It is not possible for our management to predict all risks, 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 any forward-looking statements we may make. Given these risks, uncertainties and other factors, many of which are beyond our control, we cannot assure you that the forward-looking statements in this prospectus, the documents incorporated by reference herein or any free writing prospectus that we have authorized for use in connection with this offering will prove to be accurate, and you should not place undue reliance on these forward-looking statements. Furthermore, if our forward-looking statements prove to be inaccurate, the inaccuracy may be material. In light of the significant uncertainties in these forward-looking statements, you should not regard these statements as a representation or warranty by us or any other person that we will achieve our objectives and plans in any specified timeframe, or at all.

Except as required by law, we assume no obligation to update these forward-looking statements publicly, or to revise any forward-looking statements to reflect events or developments occurring after the date of this prospectus, even if new information becomes available in the future.

USE OF PROCEEDS

We will not receive any of the proceeds from the sale or other disposition of the warrant shares by the selling shareholders pursuant to this prospectus. Upon any exercise of any of the pre-funded warrants for cash, the applicable selling shareholders would pay us the exercise price set forth in the pre-funded warrants, which is a nominal amount (\$0.01 per common share). The pre-funded warrants are also exercisable on a cashless basis. If any of the pre-funded warrants are exercised on a cashless basis, we would not receive any cash payment from the applicable selling shareholders upon any such exercise of the pre-funded warrants.

We will bear the out-of-pocket costs, expenses and fees incurred in connection with the registration of the warrant shares to be sold by the selling shareholders pursuant to this prospectus. Other than registration expenses, the selling shareholders will bear underwriting discounts, commissions, placement agent fees or other similar expenses payable with respect to sales of the warrant shares.

SELLING SHAREHOLDERS

On May 21, 2021, we entered into a securities purchase agreement with the selling shareholders named in this prospectus, pursuant to which we sold pre-funded warrants to purchase up to an aggregate of 910,746 of our common shares, no par value per share, at a purchase price of \$5.48 per pre-funded warrant, on May 21, 2021, in a private placement receiving aggregate gross proceeds of approximately \$5 million. The pre-funded warrants have an exercise price of \$0.01 per common share, are exercisable immediately and may be exercised at any time, from time to time, until exercised in full, subject to certain beneficial ownership limitations. A holder (together with its affiliates and other attribution parties) may not exercise any portion of a pre-funded warrant to the extent that immediately prior to or after giving effect to such exercise the holder would own more than 9.99% of our outstanding common shares immediately after exercise, which percentage may be changed at the holder's election to a lower or higher percentage upon 61 days' notice to us, subject to the terms of the pre-funded warrants.

Under the terms of the securities purchase agreement, we also agreed to file a registration statement within 30 days after the closing of the private placement to register for resale the shares underlying the pre-funded warrants and generally to cause the applicable registration statements to be declared effective as soon as practicable.

The selling shareholders may sell some, all or none of the common shares that may be issued to them upon exercise of the pre-funded warrants. We refer to these common shares as warrant shares. We do not know how long the selling shareholders will hold the warrant shares before selling them, and we currently have no agreements, arrangements or understandings with the selling shareholders regarding the sale or other disposition of any of the warrant shares. The warrant shares covered hereby may be offered from time to time by the selling shareholders. As a result, we cannot estimate the number of common shares each of the selling shareholders will beneficially own after termination of sales under this prospectus. In addition, each of the selling shareholders may have sold, transferred or otherwise disposed of all or a portion of its common shares since the date on which it provided information for this table.

Beneficial ownership is determined in accordance with the rules of the SEC and includes voting or investment power with respect to our common shares. Generally, a person "beneficially owns" our common shares if the person has or shares with others the right to vote those shares or to dispose of them, or if the person has the right to acquire voting or disposition rights within 60 days.

The information in the table below and the footnotes thereto regarding common shares to be beneficially owned after the offering assumes the exercise and sale of all warrant shares being offered by the selling shareholders under this prospectus. The percentage of shares owned prior to the offering is based on 29,846,000 common shares outstanding as of August 9, 2021. The percentage of shares owned after the offering is based on 29,846,000 common shares outstanding as of August 9, 2021 plus the maximum number of shares issuable upon exercise of the pre-funded warrants held by the named selling shareholder. This information has been obtained from the selling shareholders or in Schedules 13G or 13D and other public documents filed with the SEC. The address for the selling shareholders is c/o RTW Investments, LP, 40 10th Avenue, Floor 7, New York, NY 10014.

Name and Address ⁽¹⁾	Number of Shares Beneficially Owned Before Offering	Number of Shares Offered ⁽²⁾	Beneficial Ownership After Offering	
			Number of Shares Beneficially Owned	Percentage of Shares Beneficially Owned
Entities affiliated with RTW Investments, LP	4,315,102 ⁽¹⁾	910,746 ⁽²⁾	4,315,102	11.25%

- (1) Consists of 4,315,102 common shares beneficially owned by each of: (i) RTW Investments, LP ("RTW"), which is deemed the beneficial owner of shares held by RTW Master Fund, Ltd., RTW Venture Fund Limited and RTW Innovation Master Fund, Ltd. (the "Funds"), which are investment funds managed by RTW, and (ii) Roderick Wong, M.D., who serves as the Managing Partner and Chief Investment Officer of RTW. Dr. Wong exercises voting and dispositive control over the securities held by RTW and is therefore deemed to be a beneficial owner of securities owned or controlled by RTW.

Each of RTW and Dr. Wong disclaim beneficial ownership of the reported securities held by the Funds, except to the extent of its or his pecuniary interest therein. The number of shares beneficially owned by RTW and the Funds, in the aggregate, is limited by beneficial ownership limitations applicable to the pre-funded warrants held by the Funds, which limit the number of shares RTW and the Funds can beneficially own, following the exercise of such warrants, to a maximum of 9.99% of our outstanding common shares. As a result of such limitations, the number of shares beneficially owned does not include up to an aggregate of 8,518,257 common shares issuable upon exercise of pre-funded warrants held by the Funds, which includes 910,746 common shares issuable upon exercise of pre-funded warrants held by the Funds and offered under this prospectus.

- (2) Consists of 910,746 common shares issuable upon exercise of pre-funded warrants to purchase common shares held by the Funds and being offered under this prospectus.

PLAN OF DISTRIBUTION

The selling shareholders, which shall include donees, pledgees, transferees or other successors-in-interest selling warrant shares or interests in warrant shares received after the date of this prospectus from a selling shareholder as a gift, pledge, partnership distribution or other transfer, may, from time to time, sell, transfer or otherwise dispose of any or all of their warrant shares or interests in warrant shares on any stock exchange, market or trading facility on which the warrant shares are traded or in private transactions. These dispositions may be at fixed prices, at prevailing market prices at the time of sale, at prices related to the prevailing market price, at varying prices determined at the time of sale, or at negotiated prices.

The selling shareholders may use any one or more of the following methods when disposing of warrant shares or interests therein:

- ordinary brokerage transactions and transactions in which the broker-dealer solicits purchasers;
- block trades in which the broker-dealer will attempt to sell the warrant shares as agent, but may position and resell a portion of the block as principal to facilitate the transaction;
- purchases by a broker-dealer as principal and resale by the broker-dealer for its own account;
- an exchange distribution in accordance with the rules of the applicable exchange;
- privately negotiated transactions;
- short sales effected after the date the registration statement of which this prospectus is a part is declared effective by the SEC;
- through the writing or settlement of options or other hedging transactions, whether through an options exchange or otherwise;
- through agreements between broker-dealers and the selling shareholders to sell a specified number of such warrant shares at a stipulated price per share;
- a combination of any such methods of sale; and
- any other method permitted by applicable law.

The selling shareholders may, from time to time, pledge or grant a security interest in some or all of the warrant shares by them and, if they default in the performance of their secured obligations, the pledgees or secured parties may offer and sell the warrant shares, from time to time, under this prospectus, or under an amendment to this prospectus under Rule 424(b) or other applicable provision of the Securities Act amending the list of selling shareholders to include the pledgee, transferee or other successors in interest as selling shareholders under this prospectus. The selling shareholders also may transfer the warrant shares in other circumstances, in which case the pledgees, transferees or other successors in interest will be the selling beneficial owners for purposes of this prospectus.

In connection with the sale of warrant shares or interests therein, the selling shareholders may enter into hedging transactions with broker-dealers or other financial institutions, which may in turn engage in short sales of the warrant shares in the course of hedging the positions they assume. The selling shareholders may also sell our common shares short and deliver these securities to close out their short positions, or loan or pledge the warrant shares to broker-dealers that in turn may sell these securities. The selling shareholders may also enter into options or other transactions with broker-dealers or other financial institutions or the creation of one or more derivative securities that require the delivery to each such broker-dealer or other financial institution of warrant shares offered by this prospectus, which warrant shares such broker-dealer or other financial institution may resell pursuant to this prospectus (as supplemented or amended to reflect such transaction).

The aggregate proceeds to the selling shareholders from the sale of the warrant shares offered by them will be the purchase price of the warrant shares less discounts or commissions, if any. Each of the selling shareholders reserves the right to accept and, together with its agents from time to time, to reject, in whole or in part, any proposed purchase of warrant shares to be made directly or through agents. We will not receive

any of the proceeds from the sale of warrant shares in this offering, although we will receive the nominal exercise price upon exercise of the pre-funded warrants for the warrant shares, if such warrants are exercised for cash.

The selling shareholders also may resell all or a portion of the warrant shares in open market transactions in reliance upon Rule 144 under the Securities Act, provided that they meet the criteria and conform to the requirements of that rule.

The selling shareholders and any underwriters, broker-dealers or agents that participate in the sale of the warrant shares or interests therein may be “underwriters” within the meaning of Section 2(11) of the Securities Act. Any discounts, commissions, concessions or profit they earn on any resale of the warrant shares may be underwriting discounts and commissions under the Securities Act. Selling shareholders who are “underwriters” within the meaning of Section 2(11) of the Securities Act will be subject to the prospectus delivery requirements of the Securities Act.

To the extent required, the warrant shares to be sold, the names of the selling shareholders, the respective purchase prices and public offering prices, the names of any agents, dealer or underwriter, and any applicable commissions or discounts with respect to a particular offer will be set forth in an accompanying prospectus supplement or, if appropriate, a post-effective amendment to the registration statement that includes this prospectus.

In order to comply with the securities laws of some states, if applicable, the warrant shares may be sold in these jurisdictions only through registered or licensed brokers or dealers. In addition, in some states the warrant shares may not be sold unless it has been registered or qualified for sale or an exemption from registration or qualification requirements is available and is complied with.

We have advised the selling shareholders that the anti-manipulation rules of Regulation M under the Exchange Act may apply to sales of warrant shares in the market and to the activities of the selling shareholders and their affiliates. In addition, to the extent applicable we will make copies of this prospectus (as it may be supplemented or amended from time to time) available to the selling shareholders for the purpose of satisfying the prospectus delivery requirements of the Securities Act. The selling shareholders may indemnify any broker-dealer that participates in transactions involving the sale of the warrant shares against certain liabilities, including liabilities arising under the Securities Act.

LEGAL MATTERS

Certain legal matters in connection with this offering relating to U.S. law will be passed upon for us by Cooley LLP. The validity of the issuance of our common shares offered in this prospectus will be passed upon for us by Osler, Hoskin & Harcourt LLP, Montréal, Canada.

EXPERTS

The consolidated financial statements incorporated in this prospectus by reference to the [Annual Report on Form 10-K for the year ended December 31, 2020](#) have been so incorporated in reliance on the report of PricewaterhouseCoopers LLP, an independent registered public accounting firm, given on the authority of said firm as experts in auditing and accounting.

WHERE YOU CAN FIND ADDITIONAL INFORMATION

This prospectus is a part of a registration statement on Form S-3 that we filed with the SEC under the Securities Act and does not contain all of the information set forth or incorporated by reference in the registration statement. Whenever a reference is made in this prospectus or the accompanying prospectus supplement to any of our contracts, agreements or other documents, the reference may not be complete and you should refer to the exhibits that are a part of the registration statement or the exhibits to the reports or other documents incorporated by reference into this prospectus for a copy of such contract, agreement or other document. Because we are subject to the information reporting requirements of the Exchange Act, we file annual, quarterly and current reports, proxy statements and other information with the SEC. Our SEC filings are available to the public over the Internet at the SEC's website at www.sec.gov. We also maintain a website at www.milestonepharma.com, at which you may access these materials free of charge as soon as reasonably practicable after they are electronically filed with, or furnished to, the SEC. Information contained on or accessible through our website is not a part of this prospectus, and the inclusion of our website address in this prospectus is an inactive textual reference only.

INCORPORATION OF CERTAIN INFORMATION BY REFERENCE

The SEC allows us to “incorporate by reference” information from other documents that we file with it, which means that we can disclose important information to you by referring you to those documents. The information incorporated by reference is considered to be part of this prospectus. Information in this prospectus supersedes information incorporated by reference that we filed with the SEC prior to the date of this prospectus, while information that we file later with the SEC will automatically update and supersede the information in this prospectus. We incorporate by reference into this prospectus and the registration statement of which this prospectus is a part the information or documents listed below that we have filed with the SEC (Commission File No. 001-38899):

- [our Annual Report on Form 10-K for the year ended December 31, 2020, filed with the SEC on March 29, 2021;](#)
- [our Quarterly Report on Form 10-Q for the quarter ended March 31, 2021 and June 30, 2021 filed with the SEC on May 17, 2021](#) and August 11, 2021;
- our Current Reports on Form 8-K filed with the SEC on [March 30, 2021](#), [May 17, 2021](#), [June 2, 2021](#), and [June 21, 2021](#), to the extent the information in such reports is filed and not furnished; and
- [our definitive Proxy Statement on Schedule 14A, filed with the SEC on April 30, 2021, to the extent the information therein is filed and not furnished.](#)

Notwithstanding the statements in the preceding paragraphs, no document, report or exhibit (or portion of any of the foregoing) or any other information that we have “furnished” to the SEC pursuant to the Exchange Act shall be incorporated by reference into this prospectus.

We also incorporate by reference into this prospectus all documents (other than current reports furnished under Item 2.02 or Item 7.01 of Form 8-K and exhibits filed on such form that are related to such items) that are filed by us with the SEC pursuant to Sections 13(a), 13(c), 14 or 15(d) of the Exchange Act after the date of this prospectus but prior to the termination of the offering. These documents include periodic reports, such as Annual Reports on Form 10-K, Quarterly Reports on Form 10-Q and Current Reports on Form 8-K, as well as proxy statements.

We will provide to each person, including any beneficial owner, to whom a prospectus is delivered, without charge upon written or oral request, a copy of any or all of the documents that are incorporated by reference into this prospectus but not delivered with the prospectus, including exhibits that are specifically incorporated by reference into such documents. You should direct any requests for documents to Milestone Pharmaceuticals Inc., Attn: Company Secretary; 1111 Dr. Frederik-Philips Boulevard, Suite 420, Montréal, Québec, Canada H4M 2X6.

Any statement contained herein or in a document incorporated or deemed to be incorporated by reference into this prospectus will be deemed to be modified or superseded for purposes of the document to the extent that a statement contained in this document or any other subsequently filed document that is deemed to be incorporated by reference into this prospectus modifies or supersedes the statement.

PART II

INFORMATION NOT REQUIRED IN THE PROSPECTUS

Item 14. Other Expenses of Issuance and Distribution

The following table sets forth an estimate of the fees and expenses payable by us in connection with the sale of the securities being registered.

	<u>Amount</u>
SEC registration fees	\$ 477.85
Accounting fees and expenses	25,000.00
Legal fees and expenses	50,000.00
Miscellaneous fees and expenses	24,720.72
Total	<u>\$100,000.00</u>

Item 15. Indemnification of Directors and Officers

Under the Business Corporations Act (Québec), or the QBCA, and our bylaws, we must indemnify our current or former directors and officers, agents or any other persons who act or have acted at our request as a director or officer of a related entity, against all costs, charges and expenses reasonably incurred by such person in connection with any civil, criminal, administrative, investigative or other proceeding in which such person is involved because of his, her or its association with us or such a related entity, provided that such person meets the conditions described below. The QBCA also provides that we must also make an advance payment to such person for costs, charges and expenses reasonably incurred in connection with such a proceeding, provided, however, that such person shall repay such advance payment if he, she or it does not fulfill the conditions described below.

The QBCA provides for such indemnification if the following conditions are met:

- the person acted with honesty and loyalty in our interests, or, as the case may be, in the interests of the other entity for which the person acted as director or officer or in a similar capacity at our request;
- in the case of a proceeding that is enforced by a monetary penalty, the person had reasonable grounds for believing that his, her or its conduct was lawful; and
- the person was not judged by the court to have committed an intentional or gross fault.

In the case of actions by or on our behalf, we may make such advance payments or indemnify such persons against all costs, charges and expenses reasonably incurred by such person in connection with such actions, only if (i) the person fulfills the conditions set forth above and (ii) a court approves such advance payments or indemnification.

The QBCA and our bylaws authorize us to purchase and maintain insurance for the benefit of each of our current or former directors or officers and other agents and each person who acts or acted at our request as a director, officer or other agents or a person acting in a similar capacity, of another entity.

In addition, we have entered, or intend to enter, into separate indemnity agreements with each of our directors and officers pursuant to which we agree to indemnify and hold harmless our directors and officers against any and all liability, loss, damage, cost or expense in accordance with the terms and conditions of the QBCA and our bylaws.

We have purchased and currently intend to maintain insurance on behalf of each and every person who is or was a director or officer of our company against any loss arising from any claim asserted against him or her and incurred by him or her in any such capacity, subject to certain exclusions.

Item 16. Exhibits

Exhibit Number	Description of Document
3.1	Amended Articles of Incorporation (incorporated herein by reference to Exhibit 3.1 to the Registrant's Current Report on Form 8-K, 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, 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).
5.1	Opinion of Osler, Hoskin & Harcourt LLP.
10.1**	Securities Purchase Agreement dated May 21, 2021.
10.2**	Form of Pre-Funded Warrant to Purchase Common Shares.
23.1	Consent of PricewaterhouseCoopers LLP, Independent Registered Public Accounting Firm.
23.2	Consent of Osler, Hoskin & Harcourt LLP (included in Exhibit 5.1).
24.1**	Power of Attorney (included on signature page).

** Previously filed.

Item 17. Undertakings

- (a) The undersigned registrant hereby undertakes:
- (1) To file, during any period in which offers or sales are being made, a post-effective amendment to this registration statement:
 - (i) to include any prospectus required by Section 10(a)(3) of the Securities Act;
 - (ii) to reflect in the prospectus any facts or events arising after the effective date of the registration statement (or the most recent post-effective amendment thereof) which, individually or in the aggregate, represent a fundamental change in the information set forth in the registration statement. Notwithstanding the foregoing, any increase or decrease in volume of securities offered (if the total dollar value of securities offered would not exceed that which was registered) and any deviation from the low or high end of the estimated maximum offering range may be reflected in the form of prospectus filed with the SEC pursuant to Rule 424(b) if, in the aggregate, the changes in volume and price represent no more than a 20 percent change in the maximum aggregate offering price set forth in the "Calculation of Registration Fee" table in the effective registration statement;
 - (iii) to include any material information with respect to the plan of distribution not previously disclosed in the registration statement or any material change to such information in the registration statement;

provided, however, that paragraphs (1)(i), (1)(ii) and (1)(iii) of this section do not apply if the registration statement is on Form S-3 and the information required to be included in a post-effective amendment by those paragraphs is contained in reports filed with or furnished to the SEC by the registrant pursuant to Section 13 or Section 15(d) of the Securities Exchange Act of 1934 (the "Exchange Act") that are incorporated by reference in the registration statement, or is contained in a form of prospectus filed pursuant to Rule 424(b) that is part of the registration statement.

- (2) That, for the purpose of determining any liability under the Securities Act, each such post-effective amendment shall be deemed to be a new registration statement relating to the securities offered therein, and the offering of such securities at that time shall be deemed to be the initial bona fide offering thereof.
-

- (3) To remove from registration by means of a post-effective amendment any of the securities being registered which remain unsold at the termination of the offering.
 - (4) That, for the purpose of determining liability under the Securities Act to any purchaser:
 - (i) each prospectus filed by the registrant pursuant to Rule 424(b)(3) shall be deemed to be part of the registration statement as of the date the filed prospectus was deemed part of and included in the registration statement; and
 - (ii) each prospectus required to be filed pursuant to Rule 424(b)(2), (b)(5) or (b)(7) as part of a registration statement in reliance on Rule 430B relating to an offering made pursuant to Rule 415(a)(1)(i), (vii) or (x) for the purpose of providing the information required by Section 10(a) of the Securities Act shall be deemed to be part of and included in the registration statement as of the earlier of the date such form of prospectus is first used after effectiveness or the date of the first contract of sale of securities in the offering described in the prospectus. As provided in Rule 430B, for liability purposes of the issuer and any person that is at that date an underwriter, such date shall be deemed to be a new effective date of the registration statement relating to the securities in the registration statement to which the prospectus relates, and the offering of such securities at that time shall be deemed to be the initial bona fide offering thereof. *Provided, however,* that no statement made in a registration statement or prospectus that is part of the registration statement or made in a document incorporated or deemed incorporated by reference into the registration statement or prospectus that is part of the registration statement will, as to a purchaser with a time of contract of sale prior to such effective date, supersede or modify any statement that was made in the registration statement or prospectus that was part of the registration statement or made in any such document immediately prior to such effective date.
 - (b) The undersigned registrant undertakes that, for purposes of determining any liability under the Securities Act, each filing of the registrant's annual report pursuant to Section 13(a) or Section 15(d) of the Exchange Act (and, where applicable, each filing of an employee benefit plan's annual report pursuant to Section 15(d) of the Exchange Act) that is incorporated by reference in the registration statement shall be deemed to be a new registration statement relating to the securities offered therein, and the offering of such securities at that time shall be deemed to be the initial bona fide offering thereof.
 - (c) Insofar as indemnification for liabilities arising under the Securities Act may be permitted to directors, officers, and controlling persons of the registrant pursuant to the foregoing provisions, or otherwise, the registrant has been advised that in the opinion of the SEC such indemnification is against public policy as expressed in the Securities Act and is, therefore, unenforceable. In the event that a claim for indemnification against such liabilities (other than the payment by the registrant of expenses incurred or paid by a director, officer, or controlling person of the registrant in the successful defense of any action, suit, or proceeding) is asserted by such director, officer, or controlling person of the registrant in connection with the securities being registered, the registrant will, unless in the opinion of its counsel the matter has been settled by controlling precedent, submit to a court of appropriate jurisdiction the question whether such indemnification by it is against public policy as expressed in the Securities Act and will be governed by the final adjudication of such issue.
-

SIGNATURES

Pursuant to the requirements of the Securities Act, the registrant certifies that it has reasonable grounds to believe that it meets all of the requirements for filing on Form S-3 and has duly caused this registration statement to be signed on its behalf by the undersigned, thereunto duly authorized, in the City of Montréal, Province of Québec, Canada, on October 28, 2021.

MILESTONE PHARMACEUTICALS INC.

By: /s/ Joseph Oliveto
Joseph Oliveto
President and Chief Executive Officer

Pursuant to the requirements of the Securities Act, this registration statement has been signed by the following persons in the capacities and on the dates indicated.

<u>Signature</u>	<u>Title</u>	<u>Date</u>
<u>/s/ Joseph Oliveto</u> Joseph Oliveto	President, Chief Executive Officer and Director <i>(Principal Executive Officer)</i>	October 28, 2021
<u>*</u> Amit Hasija	Chief Financial Officer and Executive Vice President of Corporate Development <i>(Principal Financial Officer and Principal Accounting Officer)</i>	October 28, 2021
<u>*</u> Lisa M. Giles	Director	October 28, 2021
<u>*</u> Debra K. Liebert	Director	October 28, 2021
<u>*</u> Richard Pasternak, M.D.	Director	October 28, 2021
<u>*</u> Michael Tomsicek	Director	October 28, 2021
<u>*</u> Paul Truex	Director	October 28, 2021
<u>*</u> Robert J. Wills, PhD	Director	October 28, 2021

By: /s/ Joseph Oliveto
Joseph Oliveto
Attorney-in-Fact

Osler, Hoskin & Harcourt LLP
1000 De La Gauchetière Street West
Suite 2100
Montréal, Québec, Canada H3B 4W5
514.904.8100 MAIN
514.904.8101 FACSIMILE

The logo for Osler, Hoskin & Harcourt LLP, featuring the word "OSLER" in a large, serif, reddish-brown font.

Montréal

Toronto

Calgary

Ottawa

Vancouver

New York

October 28, 2021

Milestone Pharmaceuticals Inc.
1111 Dr. Frederik-Philips Boulevard
Montreal, Québec
H4M 2X6

Dear Sirs/Mesdames:

Re: Milestone Pharmaceuticals Inc. – Registration Statement on Form S-3

We have acted as Canadian counsel to Milestone Pharmaceuticals Inc. (the “**Corporation**”), a corporation governed by the *Business Corporations Act* (Québec), in connection with the preparation of an amended registration statement on Form S-3 (the “**Registration Statement**”), including a related prospectus filed with the Registration Statement (the “**Prospectus**”), covering the registration for resale of up to 910,746 common shares of the Corporation (the “**Shares**”) on behalf of the selling shareholders identified in the Prospectus issuable upon the exercise of certain pre-funded warrants sold to the selling shareholders in a private placement on May 21, 2021 (the “**Warrants**”).

We have examined the Registration Statement, the Prospectus and the Warrants and all such corporate and public records, statutes and regulations and have made such investigations and have reviewed such other documents as we have deemed relevant and necessary and have considered such questions of law as we have considered relevant and necessary in order to give the opinion hereinafter set forth. As to various questions of fact material to such opinions which were not independently established, we have relied upon a certificate of an officer of the Corporation.

In reviewing the foregoing documents and in giving this opinion, we have assumed (a) the legal capacity of all individuals, the genuineness of all signatures, the veracity of the information contained therein, the authenticity of all documents submitted to us as originals and the conformity to authentic or original documents of all documents submitted to us as certified, conformed, electronic, photostatic or facsimile copies and (b) the completeness, truth and accuracy of all facts set forth in the official public records, certificates and documents supplied by public officials or otherwise conveyed to us by public officials.

We are qualified to practice law in the Province of Québec and this opinion is rendered solely with respect to the Province of Québec and the federal laws of Canada applicable in the Province of Québec.

osler.com

Where our opinion expressed herein refers to the Shares having been issued as being “fully-paid and non-assessable” common shares of the Corporation, such opinion assumes that all required consideration (in whatever form) has been paid or provided. No opinion is expressed as to the adequacy of any consideration received.

We express no opinion to the extent that, notwithstanding the Corporation’s current reservation of the Shares as of the date hereof, future issuances of securities of the Corporation, including the Shares, and/or antidilution adjustments to outstanding securities of the Corporation, including the Warrants, may cause the Warrants to be exercisable for more common shares of the Corporation than the number that then remain authorized but unissued.

On the basis of the foregoing, we are of the opinion that the Shares, when issued and paid for upon exercise of the Warrants in accordance with the terms of the Warrants, will be will be validly issued, fully paid and non-assessable.

Our opinion is limited to the matters stated herein and no opinion is implied or may be inferred beyond the matters expressly stated. Our opinion is based on these laws as in effect on the date hereof, and we disclaim any obligation to advise you of facts, circumstances, events or developments which hereafter may be brought to our attention and which may alter, affect or modify the opinion expressed herein.

We consent to the filing of this opinion as an exhibit to the Registration Statement and to the reference to our firm under the caption “Legal Matters” in the Prospectus.

Yours very truly,

Osler, Hoskin & Harcourt LLP

Osler, Hoskin & Harcourt LLP

**Consent of Independent Registered Public Accounting Firm**

We hereby consent to the incorporation by reference in this Amendment No. 1 to the Registration Statement on Form S-3 of Milestone Pharmaceuticals Inc. of our report dated March 29, 2021 relating to the consolidated financial statements, which appears in Milestone Pharmaceuticals Inc.'s Annual Report on Form 10-K for the year ended December 31, 2020.

We also consent to the reference to us under the heading "Experts" in this Amendment No. 1 to the Registration Statement on Form S-3.

PricewaterhouseCoopers LLP

Partnership of Chartered Professional Accountants

Montreal, Quebec,
Canada October 28, 2021

PricewaterhouseCoopers LLP/ s.r.l./ s.e.n.c.r.l.
1250 Rene-Levesque Boulevard West, Suite 2500, Montr eal, Quebec, Canada H3B
4Y1 T: +1514205 5000, F: +1514 8761502, www.pwc.com/ ca

"PwC" refers to PricewaterhouseCoopers LLP /s.r.l./ s.e.n.c.r.l., an Ontario limited liability partnership.
