

Karyopharm Therapeutics Inc.
Form 424B5
May 01, 2018
Table of Contents

As Filed Pursuant to Rule 424(b)(5)
Registration No. 333-222726

The information in this preliminary prospectus supplement is not complete and may be changed. A registration statement relating to these securities has been filed with the Securities and Exchange Commission and is effective. This preliminary prospectus supplement and the accompanying prospectus are not an offer to sell these securities and they are not soliciting an offer to buy these securities in any jurisdiction where the offer or sale is not permitted.

Subject to completion, dated May 1, 2018

Preliminary prospectus supplement

(To prospectus dated February 14, 2018)

\$125,000,000

Common stock

We are offering shares of our common stock with an aggregate offering price of \$125,000,000.

Our common stock is listed on The Nasdaq Global Select Market under the symbol KPTI. On April 30, 2018, the last reported sale price of our common stock on The Nasdaq Global Select Market was \$13.08 per share.

We are an emerging growth company under federal securities laws and are subject to reduced public company disclosure standards. See Prospectus Supplement Summary Implications of Being an Emerging Growth Company.

Investing in our common stock involves a high degree of risk. Please read the information contained in and incorporated by reference under the heading Risk Factors beginning on page S-10 of this prospectus supplement and under a similar heading in our Annual Report on Form 10-K for the year ended December 31, 2017.

Neither the Securities and Exchange Commission nor any state securities commission has approved or disapproved of these securities or passed on the adequacy or accuracy of this prospectus supplement or the accompanying prospectus. Any representation to the contrary is a criminal offense.

	Per share	Total
Public Offering Price	\$	\$
Underwriting Discounts and Commissions(1)	\$	\$

Proceeds to Karyopharm Therapeutics Inc. (before expenses)	\$	\$
--	----	----

(1) See Underwriting for a description of compensation payable to the underwriters.

The underwriters expect to deliver the shares of common stock against payment on or about May , 2018. We have granted the underwriters an option for a period of 30 days to purchase additional shares of our common stock with an aggregate offering price of up to \$18,750,000. If the underwriters exercise the option in full, the total underwriting discounts and commissions payable by us will be \$ and the total proceeds to us, before expenses, will be \$.

J.P. Morgan

Jefferies

Leerink Partners

Canaccord Genuity JMP Securities H.C. Wainwright & Co. Baird

The date of this prospectus supplement is May , 2018.

Table of Contents

Table of contents

Prospectus supplement

	Page
<u>About this prospectus supplement</u>	S-1
<u>Cautionary note regarding forward-looking statements</u>	S-3
<u>Prospectus supplement summary</u>	S-5
<u>Risk factors</u>	S-10
<u>Use of proceeds</u>	S-16
<u>Dilution</u>	S-17
<u>Price range of our common stock</u>	S-18
<u>Dividend policy</u>	S-18
<u>Material U.S. federal tax considerations</u>	S-19
<u>Underwriting</u>	S-23
<u>Legal matters</u>	S-35
<u>Experts</u>	S-35
<u>Where you can find more information</u>	S-36
<u>Incorporation of certain information by reference</u>	S-37

Prospectus

	Page
<u>About this prospectus</u>	1
<u>Where you can find more information</u>	2
<u>Incorporation by reference</u>	3
<u>Forward-looking statements</u>	4
<u>Karyopharm Therapeutics Inc.</u>	6
<u>Consolidated ratios of earnings to fixed charges and ratios of earnings to combined fixed charges and preferred stock dividends</u>	7
<u>Use of proceeds</u>	8
<u>Description of debt Securities</u>	9
<u>Description of capital stock</u>	19
<u>Description of warrants</u>	27
<u>Description of units</u>	28
<u>Forms of securities</u>	29
<u>Plan of distribution</u>	31
<u>Legal matters</u>	33
<u>Experts</u>	33

Table of Contents

About this prospectus supplement

This document is in two parts and is part of the registration statement that we filed with the Securities and Exchange Commission, or the SEC, using a shelf registration process. The first part is this prospectus supplement, which describes the specific terms of this common stock offering and also adds to and updates information contained in the accompanying prospectus and the documents incorporated by reference herein. The second part, the accompanying prospectus, provides more general information. Generally, when we refer to this prospectus, we are referring to both parts of this document combined. To the extent there is a conflict between the information contained in this prospectus supplement and the information contained in the accompanying prospectus or any document incorporated by reference therein filed prior to the date of this prospectus supplement, you should rely on the information in this prospectus supplement; provided that if any statement in one of these documents is inconsistent with a statement in another document having a later date for example, a document incorporated by reference in the accompanying prospectus the statement in the document having the later date modifies or supersedes the earlier statement.

We further note that the representations, warranties and covenants made by us in any agreement that is filed as an exhibit to any document that is incorporated by reference herein were made solely for the benefit of the parties to such agreement, including, in some cases, for the purpose of allocating risk among the parties to such agreements, and should not be deemed to be a representation, warranty or covenant to you. Moreover, such representations, warranties or covenants were accurate only as of the date when made. Accordingly, such representations, warranties and covenants should not be relied on as accurately representing the current state of our affairs.

Neither we nor the underwriters have authorized anyone to provide any information other than that contained or incorporated by reference in this prospectus supplement, the accompanying prospectus or in any free writing prospectus prepared by or on behalf of us or to which we have referred you. We take no responsibility for, and can provide no assurance as to the reliability of, any other information that others may give you. The information contained in this prospectus supplement or the accompanying prospectus, or incorporated by reference herein or therein is accurate only as of the respective dates thereof, regardless of the time of delivery of this prospectus supplement and the accompanying prospectus or of any sale of our common stock. It is important for you to read and consider all information contained in this prospectus supplement and the accompanying prospectus, including the documents incorporated by reference herein and therein, in making your investment decision. You should also read and consider the information in the documents to which we have referred you in the sections entitled *Where You Can Find More Information* and *Incorporation of Certain Information by Reference* in this prospectus supplement and in the accompanying prospectus.

This prospectus supplement and the accompanying prospectus do not constitute an offer to sell, or a solicitation of an offer to purchase, the securities offered by this prospectus supplement and the accompanying prospectus in any jurisdiction to or from any person to whom or from whom it is unlawful to make such offer or solicitation of an offer in such jurisdiction. We are offering to sell, and seeking offers to buy, shares of our common stock only in jurisdictions where offers and sales are permitted. The distribution of this prospectus supplement and the accompanying prospectus and the offering of the common stock in certain jurisdictions may be restricted by law. Persons outside the United States who come into possession of this prospectus supplement and the accompanying prospectus must inform themselves about, and observe any restrictions relating to, the offering of the common stock and the distribution of this prospectus supplement and the accompanying prospectus outside the United States.

Unless otherwise stated, all references in this prospectus supplement and the accompanying prospectus to we, us, our, Karyopharm, the Company and similar designations refer, collectively, to Karyopharm Therapeutics Inc., a Delaware corporation, and, where appropriate, its consolidated subsidiaries.

Table of Contents

The trademarks and registered trademarks of Karyopharm Therapeutics Inc. and its subsidiaries referred to herein include, but are not limited to, Karyopharm Therapeutics, our logo, our name and logo used together. Third-party product and company names mentioned herein may be the trademarks of their respective owners. Solely for convenience, the trademarks and trade names in this prospectus may be referred to without the ® and ™ symbols, but such references should not be construed as any indicator that their respective owners will not assert, to the fullest extent under applicable law, their rights thereto.

No action is being taken in any jurisdiction outside the United States to permit a public offering of the securities or possession or distribution of this prospectus supplement or the accompanying prospectus in that jurisdiction. Persons who come into possession of this prospectus supplement or the accompanying prospectus in jurisdictions outside the United States are required to inform themselves about and to observe any restrictions as to this offering and the distribution of this prospectus supplement or the accompanying prospectus applicable to that jurisdiction.

S-2

Table of Contents

Cautionary note regarding forward-looking statements

This prospectus supplement, the accompanying prospectus and the information incorporated by reference herein and therein include forward-looking statements within the meaning of Section 27A of the Securities Act of 1933, as amended, or the Securities Act, and Section 21E of the Securities Exchange Act of 1934, as amended, or the Exchange Act. All statements, other than statements of historical facts, included in this prospectus supplement, the accompanying prospectus and the information incorporated by reference herein and therein regarding our strategy, future operations, future financial position, future revenue, projected costs, prospects, plans, objectives of management and expected market growth are forward-looking statements. The words anticipate, believe, estimate, expect, intend, may, plan, predict, project, potential, will, would, could, should, continue and similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words. These forward-looking statements include, among other things, statements about:

the timing, progress and results of current and future preclinical studies and clinical trials, and our research and development programs;

our plans to develop and commercialize our drug candidates;

adverse results in our preclinical and clinical development activities;

the timing or likelihood of regulatory filings and approvals;

decisions made by the U.S. Food and Drug Administration and other regulatory authorities with respect to the development and commercialization of our drug candidates;

our commercialization, marketing and manufacturing capabilities and strategy;

our ability to obtain, maintain and enforce intellectual property rights for our drug candidates;

dependence on any collaborators we may have in the future;

our competitive position;

developments and projections relating to our competitors and our industry;

our ability to obtain any necessary financing to conduct our planned activities;

our expectations regarding the time during which we will be an emerging growth company under the Jumpstart Our Business Startups Act of 2012, or the JOBS Act;

our expectations related to the use of proceeds from this offering; and

our estimates regarding expenses, future revenue, capital requirements and needs for additional financing.

We may not actually achieve the plans, intentions or expectations disclosed in our forward-looking statements, and you should not place undue reliance on our forward-looking statements. Actual results or events could differ materially from the plans, intentions and expectations disclosed in the forward-looking statements we make. We have included important factors in the cautionary statements included in this prospectus supplement, the accompanying prospectus, and the information incorporated by reference herein and therein, particularly in the Risk Factors section of this prospectus supplement and of our Annual Report on Form 10-K for the year ended December 31, 2017, which is incorporated by reference herein, that could cause actual results or events to differ materially from the forward-looking statements that we make. Our forward-looking statements do not reflect the potential impact of any future acquisitions, mergers, dispositions, joint ventures or investments that we may make.

S-3

Table of Contents

You should read this prospectus supplement, the accompanying prospectus and the information incorporated by reference herein and therein completely and with the understanding that our actual future results may be materially different from what we expect. Any forward-looking statement speaks only as of the date of this prospectus supplement. We do not assume any obligation to update any forward-looking statements, whether as a result of new information, future events or otherwise, except as required by law.

S-4

Table of Contents

Prospectus supplement summary

This summary highlights selected information contained elsewhere in this prospectus supplement and the accompanying prospectus and in the documents we incorporate by reference. This summary does not contain all of the information you should consider before investing in our common stock. You should read this entire prospectus supplement and the accompanying prospectus, including the documents incorporated by reference herein and therein, carefully, especially the risks of investing in our common stock discussed under "Risk Factors" beginning on page S-10 of this prospectus supplement and the "Risk Factors" section of our Annual Report on Form 10-K for the year ended December 31, 2017, along with our consolidated financial statements and notes to those consolidated financial statements, before making an investment decision.

Karyopharm Therapeutics Inc.

Overview

We are a clinical-stage pharmaceutical company focused on the discovery, development and subsequent commercialization of novel, first-in-class drugs directed against nuclear transport and related targets for the treatment of cancer and other major diseases. Our scientific expertise is focused on understanding the regulation of intracellular communication between the nucleus and the cytoplasm. We have discovered and are developing wholly-owned, novel, small molecule **S**elective **I**nhibitor of **N**uclear **E**xport, or SINE, compounds that inhibit the nuclear export protein XPO1. These SINE compounds represent a new class of drug candidates with a novel mechanism of action that have the potential to treat a variety of diseases in areas of unmet medical need. Our SINE compounds were the first oral XPO1 inhibitors in clinical development.

Our focus is on seeking the regulatory approval and commercialization of our lead drug candidate, selinexor (KPT-330), as an oral agent in cancer indications with significant unmet clinical need, initially for hematologic malignancies. We then plan to seek additional approvals for the use of selinexor in combination therapies to expand the patient populations that are eligible for selinexor, as well as to move selinexor towards front-line cancer therapy. We are also advancing the clinical development of selinexor in multiple solid tumor indications. To date, over 2,400 patients have been treated with oral selinexor in company- and investigator-sponsored clinical trials in advanced hematologic malignancies and solid tumors. Clinical trials evaluating selinexor include the Phase 2b **STORM (S**elinexor **T**reatment **of R**efractory **M**yeloma) study in multiple myeloma, the pivotal, randomized Phase 3 **BOSTON (B**ortezomib, **S**elinexor and **D**examethasone) study in multiple myeloma, the Phase 1b/2 **STOMP (S**elinexor and Backbone **T**reatments **of M**ultiple Myeloma **P**atients) study in combination with approved therapies in multiple myeloma, the Phase 2b **SADAL (S**elinexor **A**gainst **D**iffuse **A**ggressive **L**ymphoma) study in diffuse large B-cell lymphoma (DLBCL), and the Phase 2/3 **SEAL (S**elinexor in **A**dvanced **L**iposarcoma) study in liposarcoma.

We recently reported top-line data from the expanded cohort for the STORM study on April 30, 2018, and expect to provide top-line data from the SADAL study by the end of 2018, top-line data from the BOSTON study in 2019 and top-line data from the Phase 3 portion of the SEAL study by the end of 2019. We are also establishing the commercial infrastructure to support a potential launch of selinexor in the United States, and we intend to work with existing and potential partners to establish a commercial infrastructure outside the United States.

Since our inception, we have devoted most of our efforts to research and development, and we have not generated any revenue from the commercial sale of any drugs. To date, we have financed our operations principally through private placements of our preferred stock, proceeds from our initial public offering and follow-on offerings of common stock and cash generated from our business development activities.

Table of Contents

Recent developments

Our Phase 2b STORM study is an international, multi-center, single-arm clinical trial evaluating oral selinexor in combination with low-dose dexamethasone in heavily pretreated patients with refractory multiple myeloma. Part 2 of the STORM study enrolled 122 heavily pretreated patients with penta-refractory myeloma with 80mg oral selinexor dosed twice weekly in combination with low-dose dexamethasone (20mg twice weekly). In this study, patients with penta-refractory myeloma have previously received at least one alkylating agent, glucocorticoids, two immunomodulatory drugs (IMiDs) (Revlimid® (lenalidomide) and Pomalyst® (pomalidomide)), two proteasome inhibitors (PIs) (Velcade® (bortezomib) and Kyprolis® (carfilzomib)), and Darzalex® (daratumumab), an anti-CD38 monoclonal antibody, and have disease refractory to glucocorticoids, at least one PI, at least one IMiD, and Darzalex, with disease progression following their most recent therapy.

Regarding STORM study's primary objective, oral selinexor achieved a 25.4% overall response rate, which included two complete responses and 29 partial or very good partial responses in patients in Part 2 of the study. The median duration of response, a key secondary objective, was 4.4 months. All responses were confirmed by an Independent Review Committee.

Oral selinexor demonstrated a predictable and manageable tolerability profile, with safety results that were consistent with those previously reported from Part 1 of this study and from other selinexor studies. As anticipated, the most common adverse events (AEs) were nausea, vomiting, fatigue and reduced appetite and were primarily low grade and manageable with standard supportive care and/or dose modification. The most common hematologic AEs were Grade 3/4 cytopenias and were generally not associated with clinical sequelae. We plan to submit detailed STORM study results for presentation at an upcoming medical oncology meeting.

Selinexor has been granted Orphan Drug designation in multiple myeloma and Fast Track designation for the patient population evaluated in the STORM study. We plan to submit a New Drug Application (NDA) to the U.S. Food and Drug Administration (FDA) during the second half of 2018, with a request for accelerated approval for oral selinexor as a new treatment for patients with penta-refractory multiple myeloma. We also plan to submit a Marketing Authorization Application (MAA) to the European Medicines Agency (EMA) in early 2019 with a request for conditional approval. We believe that selinexor has advanced further in clinical development than any other agent being investigated in penta-refractory multiple myeloma.

The FDA instituted its Accelerated Approval Program to allow for expedited approval of drugs that treat serious conditions and that fill an unmet medical need based on a surrogate endpoint or an intermediate clinical endpoint thought to predict clinical benefit, like overall response rate. Accelerated approval is available only for drugs that provide a meaningful therapeutic benefit over existing treatments at the time of regulatory action regarding the application for accelerated approval, which the FDA has recently reiterated in its feedback to us. Particularly in disease areas with multiple available and potential new therapies, such as multiple myeloma, accelerated approval carries a high regulatory threshold. Consistent with its general guidance, the FDA has noted to us its preference for randomized studies geared toward full approval, which we have undertaken with the pivotal Phase 3 BOSTON study, and has reminded us that accelerated approval requires patients to have exhausted approved therapies. We recently received Fast Track designation from the FDA, which is available to therapeutics treating an unmet medical need in a serious condition. In light of this recognition that the STORM patient population represents an unmet medical need and the positive top-line data reported on April 30, 2018, we believe that the STORM study should support our request to the FDA for accelerated approval.

We believe the market for multiple myeloma therapies represents a compelling commercial opportunity. According to Global Data, the worldwide market for multiple myeloma drugs is expected to grow from annual

Table of Contents

sales of \$19.7 billion in 2018 to \$22.6 billion in 2023. We estimate the worldwide market for multiple myeloma drugs for treatment of patients with relapsed multiple myeloma is approximately two-thirds of the total market.

Certain preliminary financial results

As of March 31, 2018, we had approximately \$141.2 million in cash, cash equivalents and short- and long-term investments. This amount is unaudited and preliminary, is subject to completion of financial closing procedures that could result in changes to the amount, and does not present all information necessary for an understanding of our financial condition as of March 31, 2018.

Company information

We were incorporated under the laws of the State of Delaware in December 2008. Our executive offices are located at 85 Wells Avenue, 2nd Floor, Newton, Massachusetts 02459, and our telephone number is (617) 658-0600. Our website address is www.karyopharm.com. The information contained in, or accessible through, our website does not constitute part of this prospectus supplement. We have included our website address in this prospectus supplement solely as an inactive textual reference.

Implications of being an emerging growth company

As a company with less than \$1.07 billion in revenue during our last fiscal year, we qualify as an emerging growth company as defined in the JOBS Act. As an emerging growth company, we may take advantage of specified reduced disclosure and other requirements that are otherwise applicable generally to public companies. These provisions include:

reduced disclosure about our executive compensation arrangements;

exemption from holding the non-binding advisory votes on executive compensation, including golden parachute arrangements; and

exemption from the auditor attestation requirement in the assessment of our internal controls over financial reporting.

We have taken advantage of certain reduced reporting burdens in this prospectus supplement, the accompanying prospectus and the information incorporated by reference herein and therein. Accordingly, the information contained herein and therein may be different than the information you receive from other public companies in which you hold stock.

We will remain an emerging growth company until the earlier of (i) December 31, 2018 and (ii) the date on which we have issued more than \$1.0 billion in nonconvertible debt during the previous three years.

In addition, the JOBS Act provides that an emerging growth company can take advantage of an extended transition period for complying with new or revised accounting standards. This allows an emerging growth company to delay the adoption of certain accounting standards until those standards would otherwise apply to private companies. We have irrevocably elected not to avail ourselves of this exemption from new or revised accounting standards and, therefore, are subject to the same new or revised accounting standards as other public companies that are not emerging growth companies.

Table of Contents

The offering

Common stock offered by us \$125,000,000 of shares

Common stock to be outstanding after this offering 59,226,903 shares, which is based on an aggregate offering of \$125,000,000 of our common stock at an assumed public offering price of \$13.08 per share (the last reported sale price of our common stock on The Nasdaq Global Select Market on April 30, 2018)

Option to purchase additional shares We have granted the underwriters an option for a period of 30 days to purchase additional shares of our common stock with an aggregate offering price of up to \$18,750,000.

Use of Proceeds We estimate that the net proceeds to us from the shares sold by us to the underwriters in this offering, after deducting estimated offering expenses payable by us, will be approximately \$117.2 million. We currently intend to use the net proceeds from this offering:

to support continued clinical development of selinexor in hematologic malignancies and solid tumors as a single agent and in combination with approved and experimental therapies;

to conduct activities to support regulatory submissions for oral selinexor as a new treatment for patients with penta-refractory multiple myeloma and, if the results of the SADAL trial are positive, as a new treatment for patients with relapsed/refractory DLBCL;

to continue establishing the commercial infrastructure to support the potential launch of selinexor in the United States, including building and maintain sales, marketing and market access functions with related general and administrative capabilities;

for clinical trials of two of our pipeline drug candidates in oncology, eltanexor (KPT-8602), a second-generation SINE compound, and KPT-9274, a dual acting p21-activated kinase 4 (PAK4) allosteric modulator and nicotinamide phosphoribosyltransferase (NAMPT) inhibitor; and

for working capital and other general corporate purposes.

See [Use of Proceeds](#) for more information.

Risk Factors

Investing in our common stock involves a high degree of risk. You should read the [Risk Factors](#) section of this prospectus supplement, as well as those risk factors that are incorporated by reference in this prospectus supplement and the accompanying prospectus, for a discussion of factors to consider carefully before deciding to purchase shares of our common stock.

The Nasdaq Global Select Market
symbol KPTI

S-8

Table of Contents

The number of shares of our common stock to be outstanding after this offering is based on 49,670,328 shares of our common stock issued and outstanding as of March 31, 2018 and excludes:

8,702,552 shares of our common stock issuable upon the exercise of stock options outstanding as of March 31, 2018, at a weighted-average exercise price of \$ 13.21 per share;

228,100 shares of our common stock issuable upon the vesting of restricted stock units outstanding as of March 31, 2018; and

1,348,253 and 433,511 shares of our common stock available for future issuance, as of March 31, 2018, under our 2013 stock incentive plan and our 2013 employee stock purchase plan, respectively.

Unless otherwise indicated, this prospectus supplement reflects and assumes the following:

no exercise of outstanding stock options described above;

no purchases of shares of our common stock by our existing stockholders in this offering; and

no exercise by the underwriters of their option to purchase additional shares of our common stock.

Table of Contents

Risk factors

*Investing in our common stock involves a high degree of risk. Before investing in our common stock, you should consider carefully the risks described below and under the heading **Risk Factors** in our Annual Report on Form 10-K for the year ended December 31, 2017, filed with the SEC on March 15, 2018, which is incorporated by reference into this prospectus supplement, together with the other information contained in this prospectus supplement, the accompanying prospectus and in our other filings with the SEC that we have incorporated by reference in this prospectus supplement and the accompanying prospectus. If any of these risks occur, our business, financial condition, results of operations and future growth prospects could be materially and adversely affected. In these circumstances, the market price of our common stock could decline, and you may lose all or part of your investment.*

Risks related to our common stock and this offering

Our executive officers, directors and principal stockholders maintain the ability to control all matters submitted to stockholders for approval.

As of March 31, 2018, our executive officers, directors and a small number of stockholders own more than a majority of our outstanding common stock. As a result, if these stockholders were to choose to act together, they would be able to control all matters submitted to our stockholders for approval, as well as our management and affairs. For example, these persons, if they choose to act together, would control the election of directors and approval of any merger, consolidation or sale of all or substantially all of our assets. This concentration of voting power could delay or prevent an acquisition of our company on terms that other stockholders may desire.

Provisions in our corporate charter documents and under Delaware law could make an acquisition of us, which may be beneficial to our stockholders, more difficult and may prevent attempts by our stockholders to replace or remove our current management.

Provisions in our corporate charter and our bylaws may discourage, delay or prevent a merger, acquisition or other change in control of us that stockholders may consider favorable, including transactions in which stockholders might otherwise receive a premium for their shares. These provisions could also limit the price that investors might be willing to pay in the future for shares of our common stock, thereby depressing the market price of our common stock. In addition, because our board of directors is responsible for appointing the members of our management team, these provisions may frustrate or prevent any attempts by our stockholders to replace or remove our current management by making it more difficult for stockholders to replace members of our board of directors. Among other things, these provisions:

establish a classified board of directors such that not all members of the board are elected at one time;

allow the authorized number of our directors to be changed only by resolution of our board of directors;

limit the manner in which stockholders can remove directors from the board;

establish advance notice requirements for stockholder proposals that can be acted on at stockholder meetings and nominations to our board of directors;

require that stockholder actions must be effected at a duly called stockholder meeting and prohibit actions by our stockholders by written consent;

limit who may call stockholder meetings;

Table of Contents

authorize our board of directors to issue preferred stock without stockholder approval, which could be used to institute a poison pill that would work to dilute the stock ownership of a potential hostile acquirer, effectively preventing acquisitions that have not been approved by our board of directors; and

require the approval of the holders of at least 75% of the votes that all our stockholders would be entitled to cast to amend or repeal certain provisions of our charter or bylaws.

Moreover, because we are incorporated in Delaware, we are governed by the provisions of Section 203 of the Delaware General Corporation Law, which prohibits a person who owns in excess of 15% of our outstanding voting stock from merging or combining with us for a period of three years after the date of the transaction in which the person acquired in excess of 15% of our outstanding voting stock, unless the merger or combination is approved in a prescribed manner.

If you purchase shares of common stock in this offering, you will suffer immediate and substantial dilution in the book value of your investment.

The price per share of our common stock in this offering may exceed the net tangible book value per share of our common stock outstanding prior to this offering. Therefore, if you purchase shares of our common stock in this offering, you may pay a price per share that substantially exceeds our net tangible book value per share after this offering. To the extent shares are issued under outstanding options at exercise prices lower than the price of our common stock in this offering, you will incur further dilution. See the section entitled Dilution below for a more detailed illustration of the dilution you would incur if you participate in this offering.

You may experience future dilution as a result of future equity offerings.

In order to raise additional capital, we may in the future offer additional shares of our common stock or other securities convertible into or exchangeable for our common stock at prices that may not be the same as the price per share in this offering, including pursuant to our existing Controlled Equity Offering Sales Agreement, as amended from time to time, with Cantor Fitzgerald & Co., as sales agent, pursuant to which we may sell shares of our common stock up to a remaining aggregate offering price of \$75.0 million as of the date of this prospectus supplement. We may sell shares or other securities in any other offering at a price per share that is less than the price per share paid by investors in this offering, and investors purchasing shares or other securities in the future could have rights superior to existing stockholders. The price per share at which we sell additional shares of our common stock, or securities convertible or exchangeable for our common stock, in future transactions may be higher or lower than the price per share paid by investors in this offering.

An active trading market for our common stock may not be sustained.

Although our common stock is listed on The Nasdaq Global Select Market, an active trading market for our shares may not be sustained. If an active market for our common stock does not continue, it may be difficult for you to sell shares you purchase in this offering without depressing the market price for the shares, or at all. An inactive trading market for our common stock may also impair our ability to raise capital to continue to fund our operations by selling shares and may impair our ability to acquire other companies or technologies by using our shares as consideration.

If securities analysts do not continue to publish research or reports about our business or if they publish negative evaluations of our stock, the price of our stock could decline.

The trading market for our common stock relies in part on the research and reports that industry or financial analysts publish about us or our business. There can be no assurance that analysts will provide favorable coverage or continue to cover us. If one or more of the analysts covering our business downgrade their evaluations of our stock, the price of our stock could decline. If one or more of these analysts cease to cover our stock, we could lose visibility in the market for our stock, which in turn could cause our stock price to decline.

Table of Contents

The price of our common stock has been and may be volatile in the future and fluctuate substantially.

Our stock price has been and is likely to be volatile and may fluctuate substantially. For example, since January 1, 2015, our common stock has traded at prices per share as high as \$38.47 and as low as \$4.83. The stock market in general and the market for pharmaceutical and biotechnology companies in particular have experienced extreme volatility that has often been unrelated to the operating performance of particular companies. The market price for our common stock may be influenced by many factors, including:

the success of competitive drugs or technologies;

results of clinical trials of our drug candidates or those of our competitors;

regulatory or legal developments in the United States and other countries;

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 any of our drug candidates or clinical development programs;

the results of our efforts to discover, develop, acquire or in-license additional drug candidates or drugs;

actual or anticipated changes in estimates as to financial results, development timelines or recommendations by securities analysts;

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;

market conditions in the pharmaceutical and biotechnology sectors;

general economic, industry and market conditions; and

the other factors described in this Risk Factors section.

We could be subject to securities class action litigation.

In the past, securities class action litigation has often been brought against a company following a decline in the market price of its securities. This risk is especially relevant for us because pharmaceutical companies have experienced significant stock price volatility in recent years. If we face such litigation, it could result in substantial costs and a diversion of management's attention and our resources, which could harm our business.

We have broad discretion in the use of our cash and cash equivalents, including the net proceeds we receive in this offering, and may not use them effectively.

Our management has broad discretion to use our cash and cash equivalents, including the net proceeds we receive in this offering, to fund our operations and could spend these funds in ways that do not improve our results of operations or enhance the value of our common stock. The failure by our management to apply these funds effectively could result in financial losses that could have a material adverse effect on our business, cause the price of our common stock to decline and delay the development of our drug candidates. Pending their use to fund our operations, we may invest our cash and cash equivalents, including the net proceeds from this offering, in a manner that does not produce income or that loses value.

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

We are an emerging growth company, as defined in the JOBS Act, and may remain an emerging growth company until December 31, 2018. For so long as we remain an emerging growth company, we are permitted

S-12

Table of Contents

and intend to rely on exemptions from certain disclosure requirements that are applicable to other public companies that are not emerging growth companies. These exemptions include not being required to comply with the auditor attestation requirements of Section 404 of the Sarbanes-Oxley Act of 2002, or Section 404, 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 exemptions from the requirements of holding a nonbinding advisory vote on executive compensation and shareholder approval of any golden parachute payments not previously approved. We cannot predict whether investors will find our common stock less attractive if we rely on these exemptions. If some investors find our common stock less attractive as a result, there may be a less active trading market for our common stock and our stock price may be more volatile.

In addition, the JOBS Act provides that an emerging growth company can take advantage of an extended transition period for complying with new or revised accounting standards. This allows an emerging growth company to delay the adoption of certain accounting standards until those standards would otherwise 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 emerging growth companies.

We will continue to incur increased costs as a result of operating as a public company, and our management will need to continue to devote substantial time to compliance initiatives and corporate governance practices.

As a public company, and particularly after we are no longer an emerging growth company, we will incur significant legal, accounting and other expenses. In addition, the Sarbanes-Oxley Act of 2002 and rules subsequently implemented by the SEC and Nasdaq 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 will need to continue to devote a substantial amount of time to these compliance initiatives. Moreover, these rules and regulations will increase our legal and financial compliance costs and will make some activities more time-consuming and costly.

We cannot predict with certainty the amount of additional costs we may incur to continue to operate as a public company, nor can we predict the timing of such costs. In addition, the rules and regulations applicable to public companies are often subject to varying interpretations, in many cases due to their lack of specificity, and, as a result, their application in practice may evolve over time as new guidance is provided by regulatory and governing bodies which could result in continuing uncertainty regarding compliance matters and higher costs necessitated by ongoing revisions to disclosure and governance practices.

Pursuant to Section 404, we are required to furnish a report by our management on our internal control over financial reporting. However, while we remain an emerging growth company, we are not 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 are 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. 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 financial statements. In addition, if we identify one

Table of Contents

or more material weaknesses, it could result in an adverse reaction in the financial markets due to a loss of confidence in the reliability of our financial statements.

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

We have never declared or paid cash dividends on our capital stock. 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 may preclude us from paying dividends. As a result, capital appreciation, if any, of our common stock will be the sole source of gain for our stockholders for the foreseeable future.

Sales of a significant number of shares of our common stock in the public markets, or the perception that such sales could occur, could cause the market price of our common stock to drop significantly, even if our business is doing well.

Sales of a substantial number of shares of our common stock in the public market could occur at any time. These sales, or the perception in the market that the holders of a large number of shares intend to sell shares, could reduce the market price of our common stock. After this offering, we will have outstanding 59,226,903 shares of common stock based on 49,670,328 shares outstanding as of March 31, 2018 and an aggregate offering of \$125,000,000 of our common stock in this offering at an assumed public offering price of \$13.08 per share (the last reported sale price of our common stock on The Nasdaq Global Select Market on April 30, 2018). This includes the shares that we are selling in this offering, which may be resold in the public market immediately without restriction, unless purchased by our affiliates. Of the remaining shares, approximately 10.8 million shares are subject to a contractual lock-up with the underwriters for this offering for 45 days following the date of the underwriting agreement and approximately 1.4 million shares are subject to a contractual lock-up with the underwriters for this offering for 60 days following the date of the underwriting agreement. These shares are eligible for sale in the public market under Rule 144 of the Securities Act, subject to the volume limitations and other conditions of Rule 144, after the earlier of the expiration of, or release from, the lock-up period. The holders of these shares may at any time decide to sell their shares in the public market

Moreover, holders of an aggregate of approximately 10.5 million shares of our common stock as of March 31, 2018 have rights, subject to some conditions, to require us to file registration statements covering their shares or to include their shares in registration statements that we may file for ourselves or other stockholders. We have also registered all shares of common stock that we may issue under our equity compensation plans. As a result, these shares can be freely sold in the public market upon issuance, subject to volume limitations applicable to affiliates and the lock-up agreements described above, to the extent applicable.

Our ability to use our net operating loss carryforwards and tax credit carryforwards to offset future taxable income may be subject to certain limitations.

Under the provisions of the Internal Revenue Code of 1986, as amended, or the Code, our net operating loss and tax credit carryforwards are subject to review and possible adjustment by the Internal Revenue Service (and state tax authorities under relevant state tax rules). In addition, as a result of the Tax Cuts and Jobs Act of 2017, for U.S. federal income tax purposes, our use of net operating loss carryforwards arising in taxable years beginning after December 31, 2017 is limited to 80% of our taxable income in any future taxable year, although such losses may be carried forward indefinitely. It is uncertain how various states will respond to the newly enacted federal tax law. Furthermore, the use of net operating loss and tax credit carryforwards may become subject to an annual limitation under Sections 382 and 383 of the Code, respectively, and similar state provisions in the event of certain cumulative changes in the ownership interest of significant shareholders in excess of 50 percent over a three-year period. This could limit the amount of tax attributes that can be utilized annually to offset future taxable income or tax liabilities. The amount of the annual limitation is determined based on the value of a company immediately prior to the ownership change. Subsequent ownership changes

Table of Contents

may further affect the limitation in future years. Our company has completed several financings since its inception which resulted in an ownership change under Sections 382 and 383 of the Code. In addition, future changes in our stock ownership, including in connection with this offering, some of which are outside of our control, could result in ownership changes in the future. For these reasons, we may not be able to use some or all of our net operating loss and tax credit carryforwards, even if we attain profitability.

S-15

Table of Contents

Use of proceeds

We estimate that the net proceeds from the sale of shares of common stock to the underwriters in this offering will be approximately \$117.2 million (\$134.8 million if the underwriters' option to purchase additional shares is exercised in full), after deducting estimated offering expenses payable by us.

We currently intend to use the net proceeds from this offering:

to support continued clinical development of selinexor in hematologic malignancies and solid tumors as a single agent and in combination with approved and experimental therapies;

to conduct activities to support regulatory submissions for oral selinexor as a new treatment for patients with penta-refractory multiple myeloma and, if the results of the SADAL trial are positive, as a new treatment for patients with relapsed/refractory DLBCL;

to continue establishing the commercial infrastructure to support the potential launch of selinexor in the United States, including building and maintain sales, marketing and market access functions with related general and administrative capabilities;

for clinical trials of two of our pipeline drug candidates in oncology, eltanexor (KPT-8602), a second-generation SINE compound, and KPT-9274, a dual acting PAK4 allosteric modulator and NAMPT inhibitor; and

for working capital and other general corporate purposes.

The expected use of net proceeds from this offering represents our intentions based upon our current plans and business conditions, which could change in the future as our plans and business conditions evolve. The amounts and timing of our actual expenditures may vary significantly depending on numerous factors, including the progress of our development, feedback from regulatory authorities, the status of and results from clinical trials, as well as any collaborations that we may enter into with third parties for our drug candidates, and any unforeseen cash needs. As a result, our management will retain broad discretion over the allocation of the net proceeds from this offering. We may find it necessary or advisable to use the net proceeds from this offering for other purposes, and we will have broad discretion in the application of net proceeds.

Pending use of the proceeds as described above, we intend to invest the proceeds in a variety of capital preservation investments, including short-term, interest-bearing instruments, investment-grade and U.S. government securities.

After the completion of this offering, assuming net proceeds to us, after deducting estimated offering expenses payable by us, of \$117.2 million, we expect that our cash, cash equivalents and short- and long-term investments, will be sufficient to fund our current operating and capital expenditure plans into the third quarter of 2019. Our need for additional funds thereafter may be partially offset by cash generated from sales of drugs if selinexor receives accelerated approval and if we successfully commercialize selinexor in the United States, and from potential future payments related to collaboration or license arrangements we may seek to enter into as part of our strategy to commercialize selinexor outside the United States. Our future capital requirements will depend on many factors, including those discussed in **Liquidity and Capital Resources** **Funding Requirements** of our Annual Report on Form 10-K for the year ended December 31, 2017.

Table of Contents**Dilution**

If you invest in this offering, your ownership interest will be diluted immediately to the extent of the difference between the public offering price per share and the as-adjusted net tangible book value per share of our common stock after giving effect to this offering. We calculate net tangible book value per share by dividing the net tangible book value, which is tangible assets less total liabilities, by the number of outstanding shares of our common stock. Dilution represents the difference between the portion of the amount per share paid by purchasers of shares in this offering and the as adjusted net tangible book value per share of our common stock immediately after giving effect to this offering. Our net tangible book value as of December 31, 2017 was approximately \$129.5 million, or \$3.09 per share.

After giving effect to the sale of our common stock pursuant to this prospectus supplement and accompanying prospectus in the aggregate amount of \$125.0 million at an assumed offering price of \$13.08 per share, the last reported sale price of our common stock on The Nasdaq Global Select Market on April 30, 2018, and after deducting commissions and estimated aggregate offering expenses payable by us, our net tangible book value as of December 31, 2017 would have been \$246.7 million, or \$4.79 per share of common stock. This represents an immediate increase in the net tangible book value of \$1.70 per share to our existing stockholders and an immediate dilution in net tangible book value of \$8.29 per share to new investors. The following table illustrates this per share dilution:

Assumed offering price per share	\$ 13.08
Net tangible book value per share as of December 31, 2017	\$ 3.09
Increase per share to existing stockholders	\$ 1.70
As adjusted net tangible book value per share as of December 31, 2017 after giving effect to this offering	\$ 4.79
Dilution per share to new investors purchasing shares in this offering	\$ 8.29

The table above assumes for illustrative purposes that an aggregate of 9,556,575 shares of our common stock are sold pursuant to this prospectus supplement and the accompanying prospectus at a price of \$13.08 per share, the last reported sale price of our common stock on The Nasdaq Global Select Market on April 30, 2018, for aggregate gross proceeds of \$125.0 million. This information is supplied for illustrative purposes only.

The above discussion and table are based on 49,533,150 shares of our common stock issued and outstanding as of December 31, 2017 and excludes the following:

7,019,083 shares of our common stock issuable upon the exercise of stock options outstanding as of December 31, 2017, at a weighted-average exercise price of \$13.77 per share;

253,100 shares of our common stock issuable upon the vesting of restricted stock units outstanding as of December 31, 2017; and

726,707 and 433,511 shares of our common stock available for future issuance, as of December 31, 2017, under our 2013 stock incentive plan and our 2013 employee stock purchase plan, respectively.

To the extent that any options are exercised, new equity awards are granted under our equity incentive plans, or we otherwise issue additional shares of common stock in the future, there will be further dilution to new investors.

In addition, we may choose to raise additional capital due to market conditions or strategic considerations, even if we believe we have sufficient funds for our current or future operating plans. To the extent that additional capital is raised through the sale of equity or convertible debt securities, the issuance of these securities could result in further dilution to our stockholders.

Table of Contents**Price range of our common stock**

The following table sets forth the high and low intraday sale prices per share of our common stock, as reported on The Nasdaq Global Select Market, for the quarterly periods indicated:

	High	Low
Year ended December 31, 2016		
First Quarter	\$ 13.97	\$ 4.83
Second Quarter	\$ 10.45	\$ 6.63
Third Quarter	\$ 11.41	\$ 6.54
Fourth Quarter	\$ 10.30	\$ 6.27
Year ended December 31, 2017		
First Quarter	\$ 14.63	\$ 9.06
Second Quarter	\$ 13.19	\$ 7.48
Third Quarter	\$ 11.74	\$ 8.00
Fourth Quarter	\$ 12.56	\$ 9.00
Year ending December 31, 2018		
First Quarter	\$ 18.00	\$ 9.56
Second Quarter (through April 30, 2018)	\$ 15.39	\$ 11.89

On April 30, 2018, the last reported sale price of our common stock on The Nasdaq Global Select Market was \$13.08 per share. As of March 31, 2018, there were 11 holders of record of our common stock. The actual number of stockholders is greater than this number of record holders and includes stockholders who are beneficial owners, but whose shares are held in street name by brokers and other nominees. This number of holders of record also does not include stockholders whose shares may be held in trust by other entities.

Dividend policy

We have not declared or paid any cash dividends on our capital stock since our inception. We currently intend to retain future earnings, if any, to finance the operation and expansion of our business and do not anticipate paying any cash dividends in the foreseeable future. Payment of future dividends, if any, will be at the discretion of our board of directors and will depend on our financial condition, results of operations, capital requirements, restrictions contained in current or future financing instruments, provisions of applicable law and other factors the board deems relevant.

Table of Contents

Material U.S. federal tax considerations

The following is a discussion of material U.S. federal income and estate tax considerations applicable to non-U.S. holders with respect to their ownership and disposition of shares of our common stock. This discussion is for information only and is not tax advice. Accordingly, all prospective non-U.S. holders of our common stock should consult their own tax advisors with respect to the U.S. federal, state, local and non-U.S. tax consequences of the purchase, ownership and disposition of our common stock. For purposes of this discussion, a non-U.S. holder means a beneficial owner (other than a partnership or other pass-through entity) of our common stock who is not, for U.S. federal income tax purposes:

an individual who is a citizen or resident of the United States;

a corporation, or other entity treated as a corporation for U.S. federal income tax purposes, created or organized in the United States or under the laws of the United States or of any state thereof or the District of Columbia;

an estate, the income of which is subject to U.S. federal income tax regardless of its source; or

a trust if (1) a U.S. court is able to exercise primary supervision over the trust's administration and one or more U.S. persons have the authority to control all of the trust's substantial decisions or (2) the trust has a valid election in effect under applicable U.S. Treasury Regulations to be treated as a U.S. person.

This discussion is based on current provisions of the Code, existing and proposed U.S. Treasury Regulations promulgated thereunder, current administrative rulings and judicial decisions, all as in effect as of the date of this prospectus supplement, all of which are subject to change or to differing interpretation, possibly with retroactive effect. Any change could alter the tax consequences to non-U.S. holders described in this prospectus supplement. In addition, there can be no assurance that the Internal Revenue Service, which we refer to as the IRS, will not challenge one or more of the tax consequences described herein. We assume in this discussion that a non-U.S. holder holds shares of our common stock as a capital asset within the meaning of Section 1221 of the Code, generally property held for investment.

This discussion does not address all aspects of U.S. federal income and estate taxation that may be relevant to a particular non-U.S. holder in light of that non-U.S. holder's individual circumstances nor does it address the alternative minimum tax, the Medicare tax on net investment income, or any aspects of U.S. state, local or non-U.S. taxes. This discussion also does not consider any specific facts or circumstances that may apply to a non-U.S. holder and does not address the special tax rules applicable to particular non-U.S. holders, such as:

insurance companies;

tax-exempt organizations;

financial institutions;

brokers or dealers in securities;

pension plans;

controlled foreign corporations;

passive foreign investment companies;

owners that have elected to mark securities to market or that hold our common stock as part of a straddle, hedge, conversion transaction, synthetic security or other integrated investment;

S-19

Table of Contents

holders who have acquired our common stock through the exercise of a stock option or otherwise as compensation; and

certain U.S. expatriates.

In addition, this discussion does not address the tax treatment of partnerships or persons who hold our common stock through partnerships or other entities or arrangements that are treated as pass-through entities for U.S. federal income tax purposes. A partner in a partnership or other pass-through entity that will hold our common stock should consult his, her or its own tax advisor regarding the tax consequences of acquiring, holding and disposing of our common stock through a partnership or other pass-through entity, as applicable.

Distributions on our common stock

Distributions on our common stock generally will constitute dividends for U.S. federal income tax purposes to the extent paid from our current or accumulated earnings and profits, as determined under U.S. federal income tax principles. If a distribution exceeds our current and accumulated earnings and profits, the excess will be treated as a tax-free return of the non-U.S. holder's investment, up to such holder's tax basis in the common stock. Any remaining excess will be treated as capital gain, subject to the tax treatment described below in **Gain on Sale, Exchange or Other Taxable Disposition of Our Common Stock**. Any such distributions will also be subject to the discussions below under the sections titled **Backup Withholding and Information Reporting** and **Withholding and Information Reporting Requirements FATCA**.

Dividends paid to a non-U.S. holder generally will be subject to withholding of U.S. federal income tax at a 30% rate or such lower rate as may be specified by an applicable income tax treaty between the United States and such holder's country of residence. A non-U.S. holder of our common stock who claims the benefit of an applicable income tax treaty between the United States and such holder's country of residence generally will be required to provide a properly executed IRS Form W-8BEN or W-8BEN-E (or successor form) and satisfy applicable certification and other requirements. A non-U.S. holder that is eligible for a reduced rate of U.S. withholding tax under an income tax treaty may be able to obtain a refund or credit of any excess amounts withheld by timely filing the required information with the IRS. Non-U.S. holders are urged to consult their tax advisors regarding their entitlement to benefits under an applicable income tax treaty.

Dividends that are treated as effectively connected with a trade or business conducted by a non-U.S. holder within the United States and, if an applicable income tax treaty so provides, that are attributable to a permanent establishment or a fixed base maintained by the non-U.S. holder within the United States, are generally exempt from the 30% withholding tax if the non-U.S. holder satisfies applicable certification and disclosure requirements. However, such U.S. effectively connected income, net of specified deductions and credits, is generally taxed at the same U.S. federal income tax rates applicable to United States persons (as defined in the Code). Any U.S. effectively connected income received by a non-U.S. holder that is a corporation may also, under certain circumstances, be subject to an additional **branch profits tax** at a 30% rate or such lower rate as may be specified by an applicable income tax treaty between the United States and such holder's country of residence.

Gain on sale, exchange or other taxable disposition of our common stock

Subject to the discussions below under **Backup Withholding and Information Reporting** and **Withholding and Information Reporting Requirements FATCA**, in general, a non-U.S. holder will not be subject to any U.S. federal income tax on any gain realized upon such holder's sale, exchange or other taxable disposition of shares of our common stock unless:

the gain is effectively connected with the non-U.S. holder's conduct of a U.S. trade or business and, if an applicable income tax treaty so provides, is attributable to a permanent establishment or a fixed base

Table of Contents

maintained by such non-U.S. holder in the United States, in which case the non-U.S. holder generally will be taxed at the U.S. federal income tax rates applicable to United States persons (as defined in the Code) and, if the non-U.S. holder is a foreign corporation, the branch profits tax described above in **Distributions on Our Common Stock** also may apply;

the non-U.S. holder is a nonresident alien individual who is present in the United States for 183 days or more in the taxable year of the disposition and certain other conditions are met, in which case the non-U.S. holder will be subject to a 30% tax (or such lower rate as may be specified by an applicable income tax treaty between the United States and such holder's country of residence) on the net gain derived from the disposition, which may be offset by certain U.S. source capital losses of the non-U.S. holder, if any; or

we are, or have been, at any time during the five-year period preceding such disposition (or the non-U.S. holder's holding period, if shorter) a U.S. real property holding corporation, unless our common stock is regularly traded on an established securities market and the non-U.S. holder holds no more than 5% of our outstanding common stock, directly or indirectly, during the shorter of the 5-year period ending on the date of the disposition or the period that the non-U.S. holder held our common stock. If we are determined to be a U.S. real property holding corporation and the foregoing exception does not apply, then the non-U.S. holder generally will be taxed on its net gain derived from the disposition at the U.S. federal income tax rates applicable to United States persons (as defined in the Code). Generally, a corporation is a U.S. real property holding corporation only if the fair market value of its U.S. real property interests equals or exceeds 50% of the sum of the fair market value of its worldwide real property interests plus its other assets used or held for use in a trade or business. Although there can be no assurance, we do not believe that we are, or have been, a U.S. real property holding corporation, or that we are likely to become one in the future. No assurance can be provided that our common stock will be regularly traded on an established securities market for purposes of the rules described above.

Backup withholding and information reporting

We must report annually to the IRS and to each non-U.S. holder the gross amount of the distributions on our common stock paid to such holder and the tax withheld, if any, with respect to such distributions. Non-U.S. holders may have to comply with specific certification procedures to establish that the holder is not a United States person (as defined in the Code) in order to avoid backup withholding at the applicable rate with respect to dividends on our common stock. Generally, a non-U.S. holder will comply with such procedures if it provides a properly executed IRS Form W-8BEN or W-8BEN-E (or other applicable Form W-8) or otherwise meets documentary evidence requirements for establishing that it is a non-U.S. holder, or otherwise establishes an exemption. Dividends paid to non-U.S. holders subject to withholding of U.S. federal income tax, as described above in **Distributions on Our Common Stock**, generally will be exempt from U.S. backup withholding.

Information reporting and backup withholding will generally apply to the proceeds of a disposition of our common stock by a non-U.S. holder effected by or through the U.S. office of any broker, U.S. or foreign, unless the holder certifies its status as a non-U.S. holder and satisfies certain other requirements, or otherwise establishes an exemption. Generally, information reporting and backup withholding will not apply to a payment of disposition proceeds to a non-U.S. holder where the transaction is effected outside the United States through a non-U.S. office of a broker. However, for information reporting purposes, dispositions effected through a non-U.S. office of a broker with substantial U.S. ownership or operations generally will be treated in a manner similar to dispositions effected through a U.S. office of a broker. Non-U.S. holders should consult their own tax advisors regarding the application of the information reporting and backup withholding rules to them.

Copies of information returns may be made available to the tax authorities of the country in which the non-U.S. holder resides or is incorporated under the provisions of a specific treaty or agreement.

Table of Contents

Backup withholding is not an additional tax. Any amounts withheld under the backup withholding rules from a payment to a non-U.S. holder can be refunded or credited against the non-U.S. holder's U.S. federal income tax liability, if any, provided that an appropriate claim is timely filed with the IRS.

Withholding and information reporting requirements FATCA

Sections 1471 to 1474 of the Code (referred to as the Foreign Account Tax Compliance Act, or FATCA) generally impose a U.S. federal withholding tax at a rate of 30% on payments of dividends on, and gross proceeds from the sale or other disposition of, our common stock paid to certain foreign entities, unless (i) if the foreign entity is a foreign financial institution, such foreign entity undertakes certain due diligence, reporting, withholding, and certification obligations, (ii) if the foreign entity is not a foreign financial institution, such foreign entity identifies certain of its U.S. investors, if any, or (iii) the foreign entity is otherwise exempt under FATCA. Withholding under FATCA generally applies (1) to payments of dividends on our common stock and (2) to payments of gross proceeds from a sale or other disposition of our common stock made after December 31, 2018. An intergovernmental agreement between the United States and an applicable foreign country may modify the FATCA rules described above. Non-U.S. holders should consult their own tax advisors regarding the possible implications of FATCA on non-U.S. holders' investment in our common stock and the entities (including financial intermediaries) through which they hold our common stock.

U.S. federal estate tax

Shares of our common stock that are owned or treated as owned at the time of death by an individual who is not a citizen or resident of the United States, as specifically defined for U.S. federal estate tax purposes, are considered U.S. situs assets and will be included in the individual's gross estate for U.S. federal estate tax purposes. Such shares, therefore, may be subject to U.S. federal estate tax, unless an applicable estate tax or other treaty provides otherwise.

The preceding discussion of material U.S. federal tax considerations is for information only. It is not tax advice. Prospective investors should consult their own tax advisors regarding the particular U.S. federal, state, local, and non-U.S. tax consequences of purchasing, owning, and disposing of our common stock, including the consequences of any proposed changes in applicable laws.

Table of Contents**Underwriting**

We are offering the shares of common stock described in this prospectus supplement through a number of underwriters. J.P. Morgan Securities LLC, Jefferies LLC and Leerink Partners LLC are acting as joint book-running managers of the offering and as representatives of the underwriters. We have entered into an underwriting agreement with the underwriters. Subject to the terms and conditions of the underwriting agreement, we have agreed to sell to the underwriters, and each underwriter has severally agreed to purchase, at the public offering price less the underwriting discounts and commissions set forth on the cover page of this prospectus supplement, the number of shares of common stock listed next to its name in the following table:

Name	Number of shares
J.P. Morgan Securities LLC	
Jefferies LLC	
Leerink Partners LLC	
Canaccord Genuity LLC	
JMP Securities LLC	
H.C. Wainwright & Co., LLC	
Robert W. Baird & Co. Incorporated	

Total

The underwriters are committed to purchase all the common shares offered by us if they purchase any shares. The underwriting agreement also provides that if an underwriter defaults, the purchase commitments of non-defaulting underwriters may also be increased or the offering may be terminated.

The underwriters propose to offer the common shares directly to the public at the initial public offering price set forth on the cover page of this prospectus supplement and to certain dealers at that price less a concession not in excess of \$ per share. Any such dealers may resell shares to certain other brokers or dealers at a discount of up to \$ per share from the initial public offering price. After the initial offering of the shares to the public, if all of the common shares are not sold at the initial public offering price, the underwriters may change the offering price and the other selling terms. Sales of shares made outside of the United States may be made by affiliates of the underwriters.

The underwriters have an option to buy up to \$18,750,000 of additional shares of common stock from us to cover sales of shares by the underwriters which exceed the number of shares specified in the table above. The underwriters have 30 days from the date of this prospectus supplement to exercise this option to purchase additional shares. If any shares are purchased with this option to purchase additional shares, the underwriters will purchase shares in approximately the same proportions as shown in the table above. If any additional shares of common stock are purchased, the underwriters will offer the additional shares on the same terms as those on which the shares are being offered.

Table of Contents

The underwriting fee is equal to the public offering price per share of common stock less the amount paid by the underwriters to us per share of common stock. The underwriting fee is \$ _____ per share. The following table shows the per share and total underwriting discounts and commissions to be paid to the underwriters assuming both no exercise and full exercise of the underwriters' option to purchase additional shares.

	Without option to purchase additional shares exercise	With full option to purchase additional shares exercise
Per Share	\$	\$
Total	\$	\$

We estimate that the total expenses of this offering, including registration, filing and listing fees, printing fees and legal and accounting expenses, but excluding the underwriting discounts and commissions, will be approximately \$300,000. We have agreed to reimburse the underwriters for certain expenses related to Financial Industry Regulatory Authority, Inc. matters and qualification of the securities offered by this prospectus supplement under applicable state and foreign securities laws, in an amount up to \$20,000.

A prospectus in electronic format may be made available on the websites maintained by one or more underwriters, or selling group members, if any, participating in the offering. The underwriters may agree to allocate a number of shares to underwriters and selling group members for sale to their online brokerage account holders. Internet distributions will be allocated by the representatives to underwriters and selling group members that may make Internet distributions on the same basis as other allocations.

Our executive officers and directors, as well as three of our largest stockholders, Chione Ltd., Delphi BioInvestments VIII, L.P. and Delphi Ventures VIII, L.P., have agreed not to sell or transfer any common stock, or securities convertible into or exchangeable or exercisable for common stock, for 60 days (or 45 days in the case of Chione Ltd., Delphi BioInvestments VIII, L.P. and Delphi Ventures VIII, L.P.) after the date of the underwriting agreement without first obtaining the written consent of the representatives. We have agreed not to sell or transfer any common stock, or securities convertible into or exchangeable or exercisable for common stock, for 60 days after the date of the underwriting agreement without first obtaining the written consent of the representatives. Specifically, we and these other persons have agreed, with certain limited exceptions, including an exception for sales by directors and officers pursuant to existing trading plans that comply with Rule 10b5-1 under the Exchange Act, not directly or indirectly to

offer, pledge, sell or contract to sell any common stock;

sell any option or contract to purchase any common stock;

purchase any option or contract to sell any common stock;

grant any option, right or warrant for the sale of any common stock;

otherwise dispose of or transfer any common stock;

file any registration statement related to the common stock or exercise any right with respect to the registration of common stock, as applicable;

Edgar Filing: Karyopharm Therapeutics Inc. - Form 424B5

publicly announce an intention to do any of the foregoing; or

enter into any swap or other agreement or any transaction that transfers, in whole or in part, the economic consequence of ownership of any common stock, whether any such swap or other transaction described above is to be settled by delivery of shares or other securities, in cash or otherwise.

S-24

Table of Contents

This lock-up provision applies to common stock and to securities convertible into or exchangeable or exercisable for common stock. It applies to common stock owned now or acquired later by executive officers, directors and significant stockholders executing the agreements or for which such persons later acquire the power of disposition. The lock-up provision with respect to our director Deepika Pakianathan, Ph.D., who is a Managing Member at Delphi Ventures, shall not apply to any common stock, or securities convertible into or exchangeable or exercisable for common stock, held by Delphi BioInvestments VIII, L.P. or Delphi Ventures VIII, L.P., which are covered by separate lock-up agreements with such stockholders.

We have agreed to indemnify the underwriters against certain liabilities, including liabilities under the Securities Act.

Our common stock is listed on The Nasdaq Global Select Market under the symbol **KPTI**.

In connection with this offering, the underwriters may engage in stabilizing transactions, which involves making bids for, purchasing and selling shares of common stock in the open market for the purpose of preventing or retarding a decline in the market price of the common stock while this offering is in progress. These stabilizing transactions may include making short sales of the common stock, which involves the sale by the underwriters of a greater number of shares of common stock than they are required to purchase in this offering, and purchasing shares of common stock on the open market to cover positions created by short sales. Short sales may be covered shorts, which are short positions in an amount not greater than the underwriters' option to purchase additional shares referred to above, or may be naked shorts, which are short positions in excess of that amount. The underwriters may close out any covered short position either by exercising their option to purchase additional shares, in whole or in part, or by purchasing shares in the open market. In making this determination, the underwriters will consider, among other things, the price of shares available for purchase in the open market compared to the price at which the underwriters may purchase shares through the option to purchase additional shares. A naked short position is more likely to be created if the underwriters are concerned that there may be downward pressure on the price of the common stock in the open market that could adversely affect investors who purchase in this offering. To the extent that the underwriters create a naked short position, they will purchase shares in the open market to cover the position.

The underwriters have advised us that, pursuant to Regulation M of the Securities Act, they may also engage in other activities that stabilize, maintain or otherwise affect the price of the common stock, including the imposition of penalty bids. This means that if the representatives of the underwriters purchase common stock in the open market in stabilizing transactions or to cover short sales, the representatives can require the underwriters that sold those shares as part of this offering to repay the underwriting discount received by them.

These activities may have the effect of raising or maintaining the market price of the common stock or preventing or retarding a decline in the market price of the common stock, and, as a result, the price of the common stock may be higher than the price that otherwise might exist in the open market. If the underwriters commence these activities, they may discontinue them at any time. The underwriters may carry out these transactions on The Nasdaq Global Select Market, in the over-the-counter market or otherwise.

In addition, in connection with this offering certain of the underwriters (and selling group members) may engage in passive market making transactions in our common stock on The Nasdaq Global Select Market prior to the pricing and completion of this offering. Passive market making consists of displaying bids on The Nasdaq Global Select Market no higher than the bid prices of independent market makers and making purchases at prices no higher than these independent bids and effected in response to order flow. Net purchases by a passive market maker on each day are generally limited to a specified percentage of the passive market maker's average daily trading volume in the common stock during a specified period and must be discontinued when

Table of Contents

such limit is reached. Passive market making may cause the price of our common stock to be higher than the price that otherwise would exist in the open market in the absence of these transactions. If passive market making is commenced, it may be discontinued at any time.

Certain of the underwriters and their affiliates have provided in the past to us and our affiliates and may provide from time to time in the future certain commercial banking, financial advisory, investment banking and other services for us and such affiliates in the ordinary course of their business, for which they have received and may continue to receive customary fees and commissions. In addition, from time to time, certain of the underwriters and their affiliates may effect transactions for their own account or the account of customers, and hold on behalf of themselves or their customers, long or short positions in our debt or equity securities or loans, and may do so in the future.

Other than in the United States, no action has been taken by us or the underwriters that would permit a public offering of the securities offered by this prospectus in any jurisdiction where action for that purpose is required. The securities offered by this prospectus may not be offered or sold, directly or indirectly, nor may this prospectus or any other offering material or advertisements in connection with the offer and sale of any such securities be distributed or published in any jurisdiction, except under circumstances that will result in compliance with the applicable rules and regulations of that jurisdiction. Persons into whose possession this prospectus comes are advised to inform themselves about and to observe any restrictions relating to the offering and the distribution of this prospectus. This prospectus does not constitute an offer to sell or a solicitation of an offer to buy any securities offered by this prospectus in any jurisdiction in which such an offer or a solicitation is unlawful.

Notice to prospective investors in the European Economic Area

In relation to each Member State of the European Economic Area (each, a Relevant Member State), no offer of shares may be made to the public in that Relevant Member State other than:

- A. to any legal entity which is a qualified investor as defined in the Prospectus Directive;
- B. to fewer than 100 or, if the Relevant Member State has implemented the relevant provision of the 2010 PD Amending Directive, 150, natural or legal persons (other than qualified investors as defined in the Prospectus Directive), as permitted under the Prospectus Directive, subject to obtaining the prior consent of the representatives; or
- C. in any other circumstances falling within Article 3(2) of the Prospectus Directive, provided that no such offer of shares shall require us or the representatives to publish a prospectus pursuant to Article 3 of the Prospectus Directive or supplement a prospectus pursuant to Article 16 of the Prospectus Directive.

Each person in a Relevant Member State who initially acquires any shares or to whom any offer is made will be deemed to have represented, acknowledged and agreed that it is a qualified investor within the meaning of the law in that Relevant Member State implementing Article 2(1)(e) of the Prospectus Directive. In the case of any shares being offered to a financial intermediary as that term is used in Article 3(2) of the Prospectus Directive, each such financial intermediary will be deemed to have represented, acknowledged and agreed that the shares acquired by it in the offer have not been acquired on a non-discretionary basis on behalf of, nor have they been acquired with a view to their offer or resale to, persons in circumstances which may give rise to an offer of any shares to the public other than their offer or resale in a Relevant Member State to qualified investors as so defined or in circumstances in which the prior consent of the representatives has been obtained to each such proposed offer or resale.

Table of Contents

We, the representatives and their affiliates will rely upon the truth and accuracy of the foregoing representations, acknowledgements and agreements.

This prospectus has been prepared on the basis that any offer of shares in any Relevant Member State will be made pursuant to an exemption under the Prospectus Directive from the requirement to publish a prospectus for offers of shares. Accordingly any person making or intending to make an offer in that Relevant Member State of shares which are the subject of the offering contemplated in this prospectus may only do so in circumstances in which no obligation arises for us or any of the underwriters to publish a prospectus pursuant to Article 3 of the Prospectus Directive in relation to such offer. Neither we nor the underwriters have authorized, nor do they authorize, the making of any offer of shares in circumstances in which an obligation arises for us or the underwriters to publish a prospectus for such offer.

For the purpose of the above provisions, the expression "an offer to the public" in relation to any shares in any Relevant Member State means the communication in any form and by any means of sufficient information on the terms of the offer and the shares to be offered so as to enable an investor to decide to purchase or subscribe the shares, as the same may be varied in the Relevant Member State by any measure implementing the Prospectus Directive in the Relevant Member State and the expression "Prospectus Directive" means Directive 2003/71/EC (including the 2010 PD Amending Directive, to the extent implemented in the Relevant Member States) and includes any relevant implementing measure in the Relevant Member State and the expression "2010 PD Amending Directive" means Directive 2010/73/EU.

Notice to prospective investors in the United Kingdom

In addition, in the United Kingdom, this document is being distributed only to, and is directed only at, and any offer subsequently made may only be directed at persons who are "qualified investors" (as defined in the Prospectus Directive) (i) who have professional experience in matters relating to investments falling within Article 19 (5) of the Financial Services and Markets Act 2000 (Financial Promotion) Order 2005, as amended, or the Order, and/or (ii) who are high net worth companies (or persons to whom it may otherwise be lawfully communicated) falling within Article 49(2)(a) to (d) of the Order (all such persons together being referred to as "relevant persons").

Any person in the United Kingdom that is not a relevant person should not act or rely on the information included in this document or use it as basis for taking any action. In the United Kingdom, any investment or investment activity that this document relates to may be made or taken exclusively by relevant persons. Any person in the United Kingdom that is not a relevant person should not act or rely on this document or any of its contents.

Notice to prospective investors in Switzerland

The shares may not be publicly offered in Switzerland and will not be listed on the SIX Swiss Exchange, or SIX, or on any other stock exchange or regulated trading facility in Switzerland. This document does not constitute a prospectus within the meaning of, and has been prepared without regard to the disclosure standards for issuance prospectuses under art. 652a or art. 1156 of the Swiss Code of Obligations or the disclosure standards for listing prospectuses under art. 27 ff. of the SIX Listing Rules or the listing rules of any other stock exchange or regulated trading facility in Switzerland. Neither this document nor any other offering or marketing material relating to the shares or the offering may be publicly distributed or otherwise made publicly available in Switzerland.

Neither this document nor any other offering or marketing material relating to the offering, us, or the shares have been or will be filed with or approved by any Swiss regulatory authority. In particular, this document will

Table of Contents

not be filed with, and the offer of shares will not be supervised by, the Swiss Financial Market Supervisory Authority FINMA, or FINMA, and the offer of shares has not been and will not be authorized under the Swiss Federal Act on Collective Investment Schemes, or CISA. The investor protection afforded to acquirers of interests in collective investment schemes under the CISA does not extend to acquirers of shares.

The shares may not be publicly offered in Switzerland and will not be listed on the SIX Swiss Exchange, or SIX, or on any other stock exchange or regulated trading facility in Switzerland. This document does not constitute a prospectus within the meaning of, and has been prepared without regard to the disclosure standards for issuance prospectuses under art. 652a or art. 1156 of the Swiss Code of Obligations or the disclosure standards for listing prospectuses under art. 27 ff. of the SIX Listing Rules or the listing rules of any other stock exchange or regulated trading facility in Switzerland. Neither this document nor any other offering or marketing material relating to the shares or the offering may be publicly distributed or otherwise made publicly available in Switzerland.

Neither this document nor any other offering or marketing material relating to the offering, us, or the shares have been or will be filed with or approved by any Swiss regulatory authority. In particular, this document will not be filed with, and the offer of shares will not be supervised by, the Swiss Financial Market Supervisory Authority FINMA, or FINMA, and the offer of shares has not been and will not be authorized under the Swiss Federal Act on Collective Investment Schemes, or CISA. The investor protection afforded to acquirers of interests in collective investment schemes under the CISA does not extend to acquirers of shares.

Notice to prospective investors in the Dubai International Financial Centre

This document relates to an Exempt Offer in accordance with the Markets Rules 2012 of the Dubai Financial Services Authority, or DFSA. This document is intended for distribution only to persons of a type specified in the Markets Rules 2012 of the DFSA. It must not be delivered to, or relied on by, any other person. The DFSA has no responsibility for reviewing or verifying any documents in connection with Exempt Offers. The DFSA has not approved this prospectus supplement nor taken steps to verify the information set forth herein and has no responsibility for this document. The securities to which this document relates may be illiquid and/or subject to restrictions on their resale. Prospective purchasers of the securities offered should conduct their own due diligence on the securities. If you do not understand the contents of this document you should consult an authorized financial advisor.

In relation to its use in the Dubai International Financial Centre, or DIFC, this document is strictly private and confidential and is being distributed to a limited number of investors and must not be provided to any person other than the original recipient, and may not be reproduced or used for any other purpose. The interests in the securities may not be offered or sold directly or indirectly to the public in the DIFC.

Notice to prospective investors in the United Arab Emirates

The shares have not been, and are not being, publicly offered, sold, promoted or advertised in the United Arab Emirates (including the DIFC) other than in compliance with the laws of the United Arab Emirates (and the DIFC) governing the issue, offering and sale of securities. Further, this prospectus supplement does not constitute a public offer of securities in the United Arab Emirates (including the DIFC) and is not intended to be a public offer. This prospectus supplement has not been approved by or filed with the Central Bank of the United Arab Emirates, the Securities and Commodities Authority or the DFSA.

Table of Contents

Notice to prospective investors in Australia

This prospectus supplement:

does not constitute a disclosure document under Chapter 6D.2 of the Corporations Act 2001 (Cth), or the Corporations Act;

has not been, and will not be, lodged with the Australian Securities and Investments Commission, or the ASIC, as a disclosure document for the purposes of the Corporations Act and does not purport to include the information required of a disclosure document under Chapter 6D.2 of the Corporations Act; and

may only be provided in Australia to select investors who are able to demonstrate that they fall within one or more of the categories of investors, or Exempt Investors, available under section 708 of the Corporations Act.

The shares may not be directly or indirectly offered for subscription or purchased or sold, and no invitations to subscribe for or buy the shares may be issued, and no draft or definitive offering memorandum, advertisement or other offering material relating to any shares may be distributed in Australia, except where disclosure to investors is not required under Chapter 6D of the Corporations Act or is otherwise in compliance with all applicable Australian laws and regulations. By submitting an application for the shares, you represent and warrant to us that you are an Exempt Investor.

As any offer of shares under this document will be made without disclosure in Australia under Chapter 6D.2 of the Corporations Act, the offer of those securities for resale in Australia within 12 months may, under section 707 of the Corporations Act, require disclosure to investors under Chapter 6D.2 if none of the exemptions in section 708 applies to that resale. By applying for the shares you undertake to us that you will not, for a period of 12 months from the date of issue of the shares, offer, transfer, assign or otherwise alienate those securities to investors in Australia except in circumstances where disclosure to investors is not required under Chapter 6D.2 of the Corporations Act or where a compliant disclosure document is prepared and lodged with ASIC.

Notice to prospective investors in Japan

The shares have not been and will not be registered under the Financial Instruments and Exchange Act. Accordingly, the none of the shares nor any interest therein may be offered or sold, directly or indirectly, in Japan or to, or for the benefit of, any resident of Japan (which term as used herein means any person resident in Japan, including any corporation or other entity organized under the laws of Japan), or to others for re-offering or resale, directly or indirectly, in Japan or to or for the benefit of a resident of Japan, except pursuant to an exemption from the registration requirements of, and otherwise in compliance with, the Financial Instruments and Exchange Act and any other applicable laws, regulations and ministerial guidelines of Japan in effect at the relevant time.

Notice to prospective investors in Hong Kong

The shares have not been offered or sold and will not be offered or sold in Hong Kong, by means of any document, other than (a) to professional investors as defined in the Securities and Futures Ordinance (Cap. 571) of Hong Kong and any rules made under that Ordinance; or (b) in other circumstances which do not result in the document being a prospectus as defined in the Companies Ordinance (Cap. 32) of Hong Kong or which do not constitute an offer to the public within the meaning of that Ordinance. No advertisement, invitation or document relating to the shares has been or may be issued or has been or may be in the possession of any person for the purposes of issue, whether in Hong Kong or elsewhere, which is directed at, or the contents of which are likely to be accessed or read by, the public of Hong Kong (except if permitted to do so under the securities laws of Hong Kong) other than with respect to shares which are or are intended to be disposed of only

Table of Contents

to persons outside Hong Kong or only to professional investors as defined in the Securities and Futures Ordinance and any rules made under that Ordinance.

The contents of this document have not been reviewed by any regulatory authority in Hong Kong. You are advised to exercise caution in relation to the offer. If you are in any doubt about any of the contents of this document, you should obtain independent professional advice.

Notice to prospective investors in Singapore

This prospectus supplement has not been registered as a prospectus with the Monetary Authority of Singapore. Accordingly, this prospectus supplement and any other document or material in connection with the offer or sale, or invitation for subscription or purchase, of shares may not be circulated or distributed, nor may the shares be offered or sold, or be made the subject of an invitation for subscription or purchase, whether directly or indirectly, to persons in Singapore other than (i) to an institutional investor under Section 274 of the Securities and Futures Act, Chapter 289 of Singapore, or the SFA, (ii) to a relevant person pursuant to Section 275(1), or any person pursuant to Section 275(1A), and in accordance with the conditions specified in Section 275, of the SFA, or (iii) otherwise pursuant to, and in accordance with the conditions of, any other applicable provision of the SFA.

Where the shares are subscribed or purchased under Section 275 of the SFA by a relevant person which is:

- a) a corporation (which is not an accredited investor (as defined in Section 4A of the SFA)) the sole business of which is to hold investments and the entire share capital of which is owned by one or more individuals, each of whom is an accredited investor; or
- b) a trust (where the trustee is not an accredited investor) whose sole purpose is to hold investments and each beneficiary of the trust is an individual who is an accredited investor, securities (as defined in Section 239(1) of the SFA) of that corporation or the beneficiaries' rights and interest (howsoever described) in that trust shall not be transferred within six months after that corporation or that trust has acquired the shares pursuant to an offer made under Section 275 of the SFA except:
 - a) to an institutional investor or to a relevant person defined in Section 275(2) of the SFA, or to any person arising from an offer referred to in Section 275(1A) or Section 276(4)(i)(B) of the SFA;
 - b) where no consideration is or will be given for the transfer;
 - c) where the transfer is by operation of law;
 - d) as specified in Section 276(7) of the SFA; or
 - e) as specified in Regulation 32 of the Securities and Futures (Offers of Investments) (Shares and Debentures) Regulations 2005 of Singapore.

Notice to prospective investors in Bermuda

Shares may be offered or sold in Bermuda only in compliance with the provisions of the Investment Business Act of 2003 of Bermuda which regulates the sale of securities in Bermuda. Additionally, non-Bermudian persons (including companies) may not carry on or engage in any trade or business in Bermuda unless such persons are permitted to do so under applicable Bermuda legislation.

Table of Contents

Notice to prospective investors in Saudi Arabia

This document may not be distributed in the Kingdom of Saudi Arabia except to such persons as are permitted under the Offers of Securities Regulations as issued by the board of the Saudi Arabian Capital Market Authority, or CMA, pursuant to resolution number 2-11-2004 dated 4 October 2004 as amended by resolution number 1-28-2008, as amended, or the CMA Regulations. The CMA does not make any representation as to the accuracy or completeness of this document and expressly disclaims any liability whatsoever for any loss arising from, or incurred in reliance upon, any part of this document. Prospective purchasers of the securities offered hereby should conduct their own due diligence on the accuracy of the information relating to the securities. If you do not understand the contents of this document, you should consult an authorised financial adviser.

Notice to prospective investors in the British Virgin Islands

The shares are not being, and may not be offered to the public or to any person in the British Virgin Islands for purchase or subscription by or on behalf of us. The shares may be offered to companies incorporated under the BVI Business Companies Act, 2004 (British Virgin Islands), but only where the offer will be made to, and received by, the relevant British Virgin Islands company entirely outside of the British Virgin Islands.

This prospectus supplement has not been, and will not be, registered with the Financial Services Commission of the British Virgin Islands. No registered prospectus has been or will be prepared in respect of the securities for the purposes of the Securities and Investment Business Act, 2010, or SIBA, or the Public Issuers Code of the British Virgin Islands.

The shares may be offered to persons located in the British Virgin Islands who are qualified investors for the purposes of SIBA. Qualified investors include (i) certain entities which are regulated by the Financial Services Commission in the British Virgin Islands, including banks, insurance companies, licensees under SIBA and public, professional and private mutual funds; (ii) a company, any securities of which are listed on a recognised exchange; and (iii) persons defined as professional investors under SIBA, which is any person (a) whose ordinary business involves, whether for that person's own account or the account of others, the acquisition or disposal of property of the same kind as the property, or a substantial part of the property of the Company; or (b) who has signed a declaration that he, whether individually or jointly with his spouse, has net worth in excess of US\$1,000,000 and that he consents to being treated as a professional investor.

Notice to prospective investors in China

This prospectus supplement does not constitute a public offer of the shares, whether by sale or subscription, in the People's Republic of China, or the PRC. The shares are not being offered or sold directly or indirectly in the PRC to or for the benefit of, legal or natural persons of the PRC.

Further, no legal or natural persons of the PRC may directly or indirectly purchase any of the shares or any beneficial interest therein without obtaining all prior PRC's governmental approvals that are required, whether statutorily or otherwise. Persons who come into possession of this document are required by the issuer and its representatives to observe these restrictions.

Notice to prospective investors in Korea

The shares have not been and will not be registered under the Financial Investments Services and Capital Markets Act of Korea and the decrees and regulations thereunder, or the FSCMA, and the shares have been and will be offered in Korea as a private placement under the FSCMA. None of the shares may be offered, sold or delivered directly or indirectly, or offered or sold to any person for re-offering or resale, directly or indirectly, in

Table of Contents

Korea or to any resident of Korea except pursuant to the applicable laws and regulations of Korea, including the FSCMA and the Foreign Exchange Transaction Law of Korea and the decrees and regulations thereunder, or the FETL. The shares have not been listed on any of securities exchanges in the world including, without limitation, the Korea Exchange in Korea. Furthermore, the purchaser of the shares shall comply with all applicable regulatory requirements (including but not limited to requirements under the FETL) in connection with the purchase of the shares. By the purchase of the shares, the relevant holder thereof will be deemed to represent and warrant that if it is in Korea or is a resident of Korea, it purchased the shares pursuant to the applicable laws and regulations of Korea.

Notice to prospective investors in Malaysia

No prospectus or other offering material or document in connection with the offer and sale of the shares has been or will be registered with the Securities Commission of Malaysia, or the Commission, for the Commission's approval pursuant to the Capital Markets and Services Act 2007. Accordingly, this prospectus supplement and any other document or material in connection with the offer or sale, or invitation for subscription or purchase, of the shares may not be circulated or distributed, nor may the shares be offered or sold, or be made the subject of an invitation for subscription or purchase, whether directly or indirectly, to persons in Malaysia other than (i) a closed end fund approved by the Commission; (ii) a holder of a Capital Markets Services Licence; (iii) a person who acquires the shares, as principal, if the offer is on terms that the shares may only be acquired at a consideration of not less than RM250,000 (or its equivalent in foreign currencies) for each transaction; (iv) an individual whose total net personal assets or total net joint assets with his or her spouse exceeds RM3 million (or its equivalent in foreign currencies), excluding the value of the primary residence of the individual; (v) an individual who has a gross annual income exceeding RM300,000 (or its equivalent in foreign currencies) per annum in the preceding twelve months; (vi) an individual who, jointly with his or her spouse, has a gross annual income of RM400,000 (or its equivalent in foreign currencies), per annum in the preceding twelve months; (vii) a corporation with total net assets exceeding RM10 million (or its equivalent in a foreign currencies) based on the last audited accounts; (viii) a partnership with total net assets exceeding RM10 million (or its equivalent in foreign currencies); (ix) a bank licensee or insurance licensee as defined in the Labuan Financial Services and Securities Act 2010; (x) an Islamic bank licensee or takaful licensee as defined in the Labuan Financial Services and Securities Act 2010; and (xi) any other person as may be specified by the Commission; provided that, in the each of the preceding categories (i) to (xi), the distribution of the shares is made by a holder of a Capital Markets Services Licence who carries on the business of dealing in securities. The distribution in Malaysia of this prospectus supplement is subject to Malaysian laws. This prospectus supplement does not constitute and may not be used for the purpose of public offering or an issue, offer for subscription or purchase, invitation to subscribe for or purchase any securities requiring the registration of a prospectus with the Commission under the Capital Markets and Services Act 2007.

Notice to prospective investors in Taiwan

The shares have not been and will not be registered with the Financial Supervisory Commission of Taiwan pursuant to relevant securities laws and regulations and may not be sold, issued or offered within Taiwan through a public offering or in circumstances which constitutes an offer within the meaning of the Securities and Exchange Act of Taiwan that requires a registration or approval of the Financial Supervisory Commission of Taiwan. No person or entity in Taiwan has been authorised to offer, sell, give advice regarding or otherwise intermediate the offering and sale of the shares in Taiwan.

Table of Contents

Notice to prospective investors in South Africa

Due to restrictions under the securities laws of South Africa, the shares are not offered, and the offer shall not be transferred, sold, renounced or delivered, in South Africa or to a person with an address in South Africa, unless one or other of the following exemptions applies:

- (i) the offer, transfer, sale, renunciation or delivery is to:
 - (a) persons whose ordinary business is to deal in securities, as principal or agent;
 - (b) the South African Public Investment Corporation;
 - (c) persons or entities regulated by the Reserve Bank of South Africa;
 - (d) authorised financial service providers under South African law;
 - (e) financial institutions recognised as such under South African law;
 - (f) a wholly-owned subsidiary of any person or entity contemplated in (c), (d) or (e), acting as agent in the capacity of an authorised portfolio manager for a pension fund or collective investment scheme (in each case duly registered as such under South African law);
or
 - (g) any combination of the person in (a) to (f); or
- (ii) the total contemplated acquisition cost of the securities, for any single addressee acting as principal is equal to or greater than ZAR1,000,000.

No offer to the public (as such term is defined in the South African Companies Act, No. 71 of 2008 (as amended or re-enacted), or South African Companies Act) in South Africa is being made in connection with the issue of the shares. Accordingly, this document does not, nor is it intended to, constitute a registered prospectus (as that term is defined in the South African Companies Act) prepared and registered under the South African Companies Act and has not been approved by, and/or filed with, the South African Companies and Intellectual Property Commission or any other regulatory authority in South Africa. Any issue or offering of the shares in South Africa constitutes an offer of the shares in South Africa for subscription or sale in South Africa only to persons who fall within the exemption from offers to the public set out in section 96(1)(a) of the South African Companies Act. Accordingly, this document must not be acted on or relied on by persons in South Africa who do not fall within section 96(1)(a) of the South African Companies Act (such persons being referred to as SA Relevant Persons). Any investment or investment activity to which this document relates is available in South Africa only to SA Relevant Persons and will be engaged in South Africa only with SA Relevant Persons.

Notice to prospective investors in Canada

The shares may be sold only to purchasers purchasing, or deemed to be purchasing, as principal that are accredited investors, as defined in National Instrument 45-106 *Prospectus Exemptions* or subsection 73.3(1) of the *Securities Act* (Ontario), and are permitted clients, as defined in National Instrument 31-103 *Registration Requirements, Exemptions and Ongoing Registrant Obligations*. Any resale of the shares must be made in accordance with an exemption from, or in a transaction not subject to, the prospectus requirements of applicable securities laws. Securities legislation in certain provinces or territories of Canada may provide a purchaser with remedies for rescission or damages if this prospectus

Edgar Filing: Karyopharm Therapeutics Inc. - Form 424B5

supplement (including any amendment thereto) contains a misrepresentation, provided that the remedies for rescission or damages are exercised by the purchaser within the time limit prescribed by the securities legislation of the purchaser's province or territory. The purchaser should refer to any applicable provisions of the securities legislation of the purchaser's province or territory for particulars of these rights or consult with a legal advisor.

S-33

Table of Contents

Pursuant to section 3A.3 (or, in the case of securities issued or guaranteed by the government of a non-Canadian jurisdiction, section 3A.4) of National Instrument 33-105 *Underwriting Conflicts* (NI 33-105), the underwriters are not required to comply with the disclosure requirements of NI 33-105 regarding underwriter conflicts of interest in connection with this offering.

S-34

Table of Contents

Legal matters

The validity of the shares of common stock offered hereby will be passed upon for us by Wilmer Cutler Pickering Hale and Dorr LLP, Boston, Massachusetts. Certain legal matters with respect to this offering will be passed upon for the underwriters by Ropes & Gray LLP, Boston, Massachusetts.

Experts

The consolidated financial statements of Karyopharm Therapeutics Inc. appearing in Karyopharm Therapeutics Inc.'s Annual Report (Form 10-K) for the year ended December 31, 2017 have been audited by Ernst & Young LLP, independent registered public accounting firm, as set forth in their report thereon, included therein, and incorporated herein by reference. Such consolidated financial statements are incorporated herein by reference in reliance upon such report given on the authority of such firm as experts in accounting and auditing.

S-35

Table of Contents

Where you can find more information

We file annual, quarterly and current reports, proxy statements and other information with the SEC pursuant to the reporting and information requirements of the Exchange Act. Our SEC filings are available to the public over the Internet at the SEC's website at <http://www.sec.gov>. Copies of certain information filed by us with the SEC are also available on our website at <http://www.karyopharm.com>. Our website is not a part of this prospectus supplement and is not incorporated by reference in this prospectus supplement. You may also read and copy any document we file at the SEC's Public Reference Room, 100 F Street, N.E., Washington, D.C. 20549. Please call the SEC at 1-800-SEC-0330 for further information on the operation of the Public Reference Room.

This prospectus supplement is part of a registration statement that we filed with the SEC. The registration statement contains more information than this prospectus supplement and the accompanying prospectus regarding us and the securities, including certain exhibits and schedules. You can obtain a copy of the registration statement from the SEC at the address listed above or from the SEC's internet site.

S-36

Table of Contents

Incorporation of certain information by reference

The SEC allows us to incorporate by reference in this prospectus supplement and the accompanying prospectus much of the information we file with the SEC, which means that we can disclose important information to you by referring you to those publicly available documents. The information that we incorporate by reference in this prospectus supplement and the accompanying prospectus is considered to be part of this prospectus supplement and the accompanying prospectus. Because we are incorporating by reference future filings with the SEC, this prospectus supplement and the accompanying prospectus is continually updated and those future filings may modify or supersede some of the information included or incorporated in this prospectus supplement and the accompanying prospectus. This means that you must look at all of the SEC filings that we incorporate by reference to determine if any of the statements in this prospectus supplement, the accompanying prospectus or in any document previously incorporated by reference have been modified or superseded. This prospectus supplement and the accompanying prospectus incorporate by reference the documents listed below (File No. 001-36167) and any future filings we make with the SEC under Sections 13(a), 13(c), 14 or 15(d) of the Exchange Act (in each case, other than those documents or the portions of those documents not deemed to be filed) until the offering of the securities under the registration statement is terminated or completed:

Annual Report on Form 10-K for the fiscal year ended December 31, 2017;

The information included in our definitive proxy statement on Schedule 14A for the 2018 Annual Meeting of Stockholders, filed on April 27, 2018, to the extent incorporated by reference into Part III of the Annual Report on Form 10-K for the fiscal year ended December 31, 2017;

Current Reports on Form 8-K filed on January 25, 2018 (both) and April 30, 2018; and

The description of our common stock contained in our Registration Statement on Form 8-A filed on November 1, 2013, including any amendments or reports filed for the purpose of updating such description.

You may request a copy of these filings, at no cost, by writing or telephoning us at the following address or phone number:

Karyopharm Therapeutics Inc.

85 Wells Avenue

2nd Floor

Newton, Massachusetts 02459

Attn: Investor Relations

(617) 658-0600

S-37

Table of Contents

Prospectus

\$250,000,000

Debt securities

Common stock

Preferred stock

Warrants

Units

We may offer and sell securities from time to time in one or more offerings of up to \$250,000,000 in aggregate offering price. This prospectus describes the general terms of these securities and the general manner in which these securities will be offered. We will provide the specific terms of these securities in supplements to this prospectus. The prospectus supplements will also describe the specific manner in which these securities will be offered and may also supplement, update or amend information contained in this document. You should read this prospectus and any applicable prospectus supplement before you invest.

We may offer these securities in amounts, at prices and on terms determined at the time of offering. The securities may be sold directly to you, through agents, or through underwriters and dealers. If agents, underwriters or dealers are used to sell the securities, we will name them and describe their compensation in a prospectus supplement.

Our common stock is listed on The NASDAQ Global Select Market under the symbol KPTI.

Investing in these securities involves certain risks. See Risk Factors included in any accompanying prospectus supplement and in the documents incorporated by reference in this prospectus for a discussion of the factors you should carefully consider before deciding to purchase these securities.

Neither the Securities and Exchange Commission nor any state securities commission has approved or disapproved of these securities or passed upon the adequacy or accuracy of this prospectus. Any representation to the contrary is a criminal offense.

The date of this prospectus is February 14, 2018

Table of Contents

Table of contents

<u>About this prospectus</u>	1
<u>Where you can find more information</u>	2
<u>Incorporation by reference</u>	3
<u>Forward-looking statements</u>	4
<u>Karyopharm Therapeutics Inc.</u>	6
<u>Consolidated ratios of earnings to fixed charges and ratios of earnings to combined fixed charges and preferred stock dividends</u>	7
<u>Use of proceeds</u>	8
<u>Description of debt securities</u>	9
<u>Description of capital stock</u>	19
<u>Description of warrants</u>	27
<u>Description of units</u>	28
<u>Forms of securities</u>	29
<u>Plan of distribution</u>	31
<u>Legal matters</u>	33
<u>Experts</u>	33

Table of Contents

About this prospectus

This prospectus is part of a registration statement that we filed with the Securities and Exchange Commission, which we refer to as the SEC, utilizing a shelf registration process. Under this shelf registration process, we may from time to time sell any combination of the securities described in this prospectus, either separately or in units, in one or more offerings for an aggregate initial offering price of up to \$250,000,000.

This prospectus provides you with a general description of the securities we may offer. Each time we sell securities, we will provide one or more prospectus supplements that will contain specific information about the terms of the offering. The prospectus supplement may also add, update or change information contained in this prospectus. You should read both this prospectus and the accompanying prospectus supplement together with the additional information described under the heading "Where You Can Find More Information" beginning on page 2 of this prospectus.

You should rely only on the information contained in or incorporated by reference in this prospectus, any accompanying prospectus supplement or in any related free writing prospectus filed by us with the SEC. We have not authorized anyone to provide you with different information. This prospectus and any accompanying prospectus supplement do not constitute an offer to sell or the solicitation of an offer to buy any securities other than the securities described in this prospectus or such accompanying prospectus supplement or an offer to sell or the solicitation of an offer to buy such securities in any circumstances in which such offer or solicitation is unlawful. You should assume that the information appearing in this prospectus, any prospectus supplement, the documents incorporated by reference and any related free writing prospectus is accurate only as of their respective dates. Our business, financial condition, results of operations and prospects may have changed materially since those dates.

Unless the context otherwise indicates, references in this prospectus to we, our and us refer, collectively, to Karyopharm Therapeutics Inc., a Delaware corporation, and its consolidated subsidiaries.

Table of Contents

Where you can find more information

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 <http://www.sec.gov>. Copies of certain information filed by us with the SEC are also available on our website at www.karyopharm.com. Our website is not a part of this prospectus and is not incorporated by reference in this prospectus. You may also read and copy any document we file at the SEC's Public Reference Room, 100 F Street, N.E., Washington, D.C. 20549. Please call the SEC at 1-800-SEC-0330 for further information on the operation of the Public Reference Room.

This prospectus is part of a registration statement we filed with the SEC. This prospectus omits some information contained in the registration statement in accordance with SEC rules and regulations. You should review the information and exhibits in the registration statement for further information about us and our consolidated subsidiaries and the securities we are offering. Statements in this prospectus concerning any document we filed as an exhibit to the registration statement or that we otherwise filed with the SEC are not intended to be comprehensive and are qualified by reference to these filings. You should review the complete document to evaluate these statements.

Table of Contents

Incorporation by reference

The SEC allows us to incorporate by reference much of the information we file with the SEC, which means that we can disclose important information to you by referring you to those publicly available documents. The information that we incorporate by reference in this prospectus is considered to be part of this prospectus. Because we are incorporating by reference future filings with the SEC, this prospectus is continually updated and those future filings may modify or supersede some of the information included or incorporated in this prospectus. This means that you must look at all of the SEC filings that we incorporate by reference to determine if any of the statements in this prospectus or in any document previously incorporated by reference have been modified or superseded. This prospectus incorporates by reference the documents listed below (File No. 001-36167) and any future filings we make with the SEC under Sections 13(a), 13(c), 14 or 15(d) of the Securities Exchange Act of 1934, as amended, or the Exchange Act (in each case, other than those documents or the portions of those documents not deemed to be filed) between the date of the initial registration statement and the effectiveness of the registration statement and following the effectiveness of the registration statement until the offering of the securities under the registration statement is terminated or completed:

Annual Report on Form 10-K for the fiscal year ended December 31, 2016, including the information specifically incorporated by reference into the Annual Report on Form 10-K from our definitive proxy statement for the 2017 Annual Meeting of Stockholders;

Quarterly Reports on Form 10-Q for the fiscal quarters ended March 31, 2017, June 30, 2017 and September 30, 2017;

Current Reports on Form 8-K filed January 26, 2017, April 3, 2017, April 4, 2017, April 5, 2017 (solely with respect to item 8.01), April 26, 2017, June 16, 2017, June 23, 2017, September 12, 2017, September 20, 2017, October 12, 2017, December 1, 2017, December 11, 2017 and January 25, 2018; and

The description of our common stock contained in our Registration Statement on Form 8-A filed on November 1, 2013, including any amendments or reports filed for the purpose of updating such description.

You may request a copy of these filings, at no cost, by writing or telephoning us at the following address or telephone number:

Karyopharm Therapeutics Inc.

85 Wells Avenue, 2nd Floor

Newton, MA 02459

Attn: Investor Relations

(617) 658-0600

Table of Contents

Forward-looking statements

This prospectus and the information incorporated by reference in this prospectus include 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 Exchange Act. All statements, other than statements of historical facts, included in this prospectus and the information incorporated by reference herein and therein regarding our strategy, future operations, future financial position, future revenue, projected costs, prospects, plans, objectives of management and expected market growth are forward-looking statements. The words anticipate, believe, estimate, expect, intend, may, plan, predict, project, target, would, could, should, continue and similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words. These forward-looking statements include, among other things, statements about:

the timing, progress and results of current and future preclinical studies and clinical trials, and our research and development programs;

our plans to develop and commercialize our drug candidates;

adverse results in our drug discovery and clinical development activities;

the timing or likelihood of regulatory filings and approvals;

decisions made by the U.S. Food and Drug Administration and other regulatory authorities with respect to the development and commercialization of our drug candidates;

our commercialization, marketing and manufacturing capabilities and strategy;

our ability to obtain, maintain and enforce intellectual property rights for our drug candidates;

dependence on our collaborators;

our intellectual property position;

our competitive position;

developments and projections relating to our competitors and our industry;

our ability to obtain any necessary financing to conduct our planned activities;

our expectations regarding the time during which we will be an emerging growth company under the Jumpstart Our Business Startups Act of 2012, or the JOBS Act; and

our estimates regarding expenses, future revenue, capital requirements and needs for additional financing. We may not actually achieve the plans, intentions or expectations disclosed in our forward-looking statements, and you should not place undue reliance on our forward-looking statements. Actual results or events could differ materially from the plans, intentions and expectations disclosed in the forward-looking statements we make. You are cautioned that these forward-looking statements are only predictions and are subject to risks, uncertainties and assumptions that are referenced in the section of any accompanying prospectus supplement entitled Risk Factors. You should also carefully review the risk factors and cautionary statements described in the other documents we file from time to time with the SEC, specifically our most recent Annual Report on Form 10-K, our Quarterly Reports on Form 10-Q and our Current Reports on Form 8-K. Our forward-looking statements do not reflect the potential impact of any future acquisitions, mergers, dispositions, joint ventures or investments that we may make.

Table of Contents

You should read this prospectus and the information incorporated by reference herein completely and with the understanding that our actual future results may be materially different from what we expect. We do not assume any obligation to update any forward-looking statements, whether as a result of new information, future events or otherwise, except as required by law.

Table of Contents

Karyopharm Therapeutics Inc.

Overview

We are a clinical-stage pharmaceutical company focused on the discovery, development and subsequent commercialization of novel, first-in-class drugs directed against nuclear transport and related targets for the treatment of cancer and other major diseases. Our scientific expertise is focused on understanding the regulation of intracellular communication between the nucleus and the cytoplasm. We have discovered and are developing wholly-owned, novel, small molecule Selective Inhibitor of Nuclear Export, or SINE, compounds that inhibit the nuclear export protein XPO1. These SINE compounds represent a new class of drug candidates with a novel mechanism of action that have the potential to treat a variety of diseases in areas of unmet medical need. Our SINE compounds were the first oral XPO1 inhibitors in clinical development.

Corporate information

We were incorporated under the laws of the State of Delaware in December 2008. Our executive offices are located at 85 Wells Avenue, Newton, Massachusetts 02459, and our telephone number is (617) 658-0600. Our website address is www.karyopharm.com. We have included our website address in this prospectus solely as an inactive textual reference. The trademarks, trade names and service marks appearing in this prospectus are the property of their respective owners.

Table of Contents

Consolidated ratios of earnings to fixed charges and ratios of earnings to combined fixed charges and preferred stock dividends

The following table sets forth our ratio of earnings to fixed charges and the ratio of earnings to combined fixed charges and preferred stock dividends for each of the periods indicated. You should read this table in conjunction with the consolidated financial statements and notes incorporated by reference in this prospectus.

	Nine months ended		Fiscal year ended			
	September 30, 2017	December 31, 2016	December 31, 2015	December 31, 2014	December 31, 2013	December 31, 2012
Consolidated ratios of earnings to fixed charges	N/A	N/A	N/A	N/A	N/A	N/A
Consolidated ratios of earnings to combined fixed charges and preferred stock dividends	N/A	N/A	N/A	N/A	N/A	N/A

For purposes of calculating the ratios above, earnings (loss) consist of net loss. Fixed charges include interest expense on indebtedness (of which there was none) and an estimate of interest expense within rental expense.

Our earnings were insufficient to cover fixed charges in such periods and we are unable to disclose a ratio of earnings to fixed charges for such periods. Due to our losses for the nine months ended September 30, 2017 and the fiscal years ended December 31, 2016, 2015, 2014, 2013 and 2012, the ratio coverage was less than 1:1. We would have needed to generate additional earnings of \$91.1 million, \$110.7 million, \$119.1 million, \$75.8 million, \$34.0 million and \$15.9 million, respectively, to achieve a coverage ratio of 1:1 in those periods.

We have not had any shares of preferred stock outstanding since the completion of our initial public offering in November 2013.

Table of Contents

Use of proceeds

We intend to use the net proceeds from the sale of any securities offered under this prospectus for general corporate purposes unless otherwise indicated in the applicable prospectus supplement. General corporate purposes may include research and development expenditures, the acquisition or licensing of other products, businesses or technologies, working capital and capital expenditures. We have not determined the amount of net proceeds to be used specifically for such purposes. As a result, management will retain broad discretion over the allocation of net proceeds.

Table of Contents

Description of debt securities

We may offer debt securities which may be senior or subordinated. We refer to the senior debt securities and the subordinated debt securities collectively as debt securities. The following description summarizes the general terms and provisions of the debt securities. We will describe the specific terms of the debt securities and the extent, if any, to which the general provisions summarized below apply to any series of debt securities in the prospectus supplement relating to the series and any applicable free writing prospectus that we authorize to be delivered. When we refer to the Company, we, our, and us in this section, we mean Karyopharm Therapeutics Inc. excluding, unless the context otherwise requires or as otherwise expressly stated, our subsidiaries.

We may issue senior debt securities from time to time, in one or more series under a senior indenture to be entered into between us and a senior trustee to be named in a prospectus supplement, which we refer to as the senior trustee. We may issue subordinated debt securities from time to time, in one or more series under a subordinated indenture to be entered into between us and a subordinated trustee to be named in a prospectus supplement, which we refer to as the subordinated trustee. The forms of senior indenture and subordinated indenture are filed as exhibits to the registration statement of which this prospectus forms a part. The senior indenture and the subordinated indenture are referred to individually as an indenture and together as the indentures and the senior trustee and the subordinated trustee are referred to individually as a trustee and together as the trustees. This section summarizes some of the provisions of the indentures and is qualified in its entirety by the specific text of the indentures, including definitions of terms used in the indentures. Wherever we refer to particular sections of, or defined terms in, the indentures, those sections or defined terms are incorporated by reference in this prospectus or the applicable prospectus supplement. You should review the indentures that are filed as exhibits to the registration statement of which this prospectus forms a part for additional information.

Neither indenture will limit the amount of debt securities that we may issue. The applicable indenture will provide that debt securities may be issued up to an aggregate principal amount authorized from time to time by us and may be payable in any currency or currency unit designated by us or in amounts determined by reference to an index.

General

The senior debt securities will constitute our unsecured and unsubordinated general obligations and will rank equally in right of payment with our other unsecured and unsubordinated obligations. The subordinated debt securities will constitute our unsecured and subordinated general obligations and will be junior in right of payment to our senior indebtedness (including senior debt securities), as described under the heading

Certain Terms of the Subordinated Debt Securities Subordination. The debt securities will be structurally subordinated to all existing and future indebtedness and other liabilities of our subsidiaries unless such subsidiaries expressly guarantee such debt securities.

The debt securities will be our unsecured obligations. Any secured debt or other secured obligations will be effectively senior to the debt securities to the extent of the value of the assets securing such debt or other obligations.

The applicable prospectus supplement and/or free writing prospectus will include any additional or different terms of the debt securities of any series being offered, including the following terms:

the title and type of the debt securities;

Table of Contents

whether the debt securities will be senior or subordinated debt securities, and, with respect to any subordinated debt securities the terms on which they are subordinated;

the initial aggregate principal amount of the debt securities;

the price or prices at which we will sell the debt securities;

the maturity date or dates of the debt securities and the right, if any, to extend such date or dates;

the rate or rates, if any, at which the debt securities will bear interest, or the method of determining such rate or rates;

the date or dates from which such interest will accrue, the interest payment dates on which such interest will be payable or the method of determination of such dates;

the right, if any, to extend the interest payment periods and the duration of that extension;

the manner of paying principal and interest and the place or places where principal and interest will be payable;

provisions for a sinking fund, purchase fund or other analogous fund, if any;

any redemption dates, prices, obligations and restrictions on the debt securities;

the currency, currencies or currency units in which the debt securities will be denominated and the currency, currencies or currency units in which principal and interest, if any, on the debt securities may be payable;

any conversion or exchange features of the debt securities;

whether the debt securities will be subject to the defeasance provisions in the indenture;

whether the debt securities will be issued in definitive or global form or in definitive form only upon satisfaction of certain conditions;

whether the debt securities will be guaranteed as to payment or performance;

any special tax implications of the debt securities;

Edgar Filing: Karyopharm Therapeutics Inc. - Form 424B5

any events of defaults or covenants in addition to or in lieu of those set forth in the indenture; and

any other material terms of the debt securities.

When we refer to "principal" in this section with reference to the debt securities, we are also referring to "premium, if any."

We may from time to time, without notice to or the consent of the holders of any series of debt securities, create and issue further debt securities of any such series ranking equally with the debt securities of such series in all respects (or in all respects other than (1) the payment of interest accruing prior to the issue date of such further debt securities or (2) the first payment of interest following the issue date of such further debt securities). Such further debt securities may be consolidated and form a single series with the debt securities of such series and have the same terms as to status, redemption or otherwise as the debt securities of such series.

You may present debt securities for exchange and you may present debt securities for transfer in the manner, at the places and subject to the restrictions set forth in the debt securities and the applicable prospectus supplement. We will provide you those services without charge, although you may have to pay any tax or other governmental charge payable in connection with any exchange or transfer, as set forth in the indenture.

Table of Contents

Debt securities may bear interest at a fixed rate or a floating rate. Debt securities bearing no interest or interest at a rate that at the time of issuance is below the prevailing market rate (original issue discount securities) may be sold at a discount below their stated principal amount. U.S. federal income tax considerations applicable to any such discounted debt securities or to certain debt securities issued at par which are treated as having been issued at a discount for U.S. federal income tax purposes will be described in the applicable prospectus supplement.

We may issue debt securities with the principal amount payable on any principal payment date, or the amount of interest payable on any interest payment date, to be determined by reference to one or more currency exchange rates, securities or baskets of securities, commodity prices or indices. You may receive a payment of principal on any principal payment date, or a payment of interest on any interest payment date, that is greater than or less than the amount of principal or interest otherwise payable on such dates, depending on the value on such dates of the applicable currency, security or basket of securities, commodity or index. Information as to the methods for determining the amount of principal or interest payable on any date, the currencies, securities or baskets of securities, commodities or indices to which the amount payable on such date is linked and certain related tax considerations will be set forth in the applicable prospectus supplement.

Certain terms of the senior debt securities

Covenants. Unless we indicate otherwise in a prospectus supplement with respect to a particular series of senior debt securities, the senior debt securities will not contain any financial or restrictive covenants, including covenants restricting either us or any of our subsidiaries from incurring, issuing, assuming or guaranteeing any indebtedness secured by a lien on any of our or our subsidiaries' property or capital stock, or restricting either us or any of our subsidiaries from entering into sale and leaseback transactions.

Consolidation, merger and sale of assets. Unless we indicate otherwise in a prospectus supplement with respect to a particular series of senior debt securities, we may not consolidate with or merge into any other person, in a transaction in which we are not the surviving corporation, or convey, transfer or lease our properties and assets substantially as an entirety to any person, in either case, unless:

the successor entity, if any, is a U.S. corporation, limited liability company, partnership or trust;

the successor entity assumes our obligations on the senior debt securities and under the senior indenture;

immediately after giving effect to the transaction, no default or event of default shall have occurred and be continuing; and

we have delivered to the senior trustee an officer's certificate and an opinion of counsel, each stating that the consolidation, merger, conveyance, transfer or lease and, if a supplemental indenture is required in connection with such transaction, such supplemental indenture, comply with the senior indenture and all conditions precedent provided for in the senior indenture relating to such transaction have been complied with.

The restrictions described in the bullets above do not apply (1) to our consolidation with or merging into one of our affiliates, if our board of directors determines in good faith that the purpose of the consolidation or merger is principally to change our state of incorporation or our form of organization to another form or (2) if we merge with or into a single direct or indirect wholly-owned subsidiary of ours.

The surviving business entity will succeed to, and be substituted for, us under the senior indenture and the senior debt securities and, except in the case of a lease, we shall be released from all obligations under the senior indenture and the senior debt securities.

Table of Contents

No protection in the event of a change in control. Unless we indicate otherwise in a prospectus supplement with respect to a particular series of senior debt securities, the senior debt securities will not contain any provisions that may afford holders of the senior debt securities protection in the event we have a change in control or in the event of a highly leveraged transaction (whether or not such transaction results in a change in control).

Events of default. Unless we indicate otherwise in a prospectus supplement with respect to a particular series of senior debt securities, the following are events of default under the senior indenture with respect to senior debt securities of each series:

failure to pay interest on any senior debt securities of such series when due and payable, if that default continues for a period of 30 days (or such other period as may be specified for such series);

failure to pay principal on the senior debt securities of such series when due and payable whether at maturity, upon redemption, by declaration or otherwise (and, if specified for such series, the continuance of such failure for a specified period);

default in the performance of or breach of any of our covenants or agreements in the senior indenture applicable to senior debt securities of such series, other than a covenant breach which is specifically dealt with elsewhere in the senior indenture, and that default or breach continues for a period of 90 days after we receive written notice from the trustee or from the holders of 25% or more in aggregate principal amount of the senior debt securities of such series;

certain events of bankruptcy or insolvency, whether or not voluntary; and

any other event of default provided for in such series of senior debt securities as may be specified in the applicable prospectus supplement. The default by us under any other debt, including any other series of debt securities, is not a default under the senior indenture.

If an event of default other than an event of default specified in the fourth bullet point above occurs with respect to a series of senior debt securities and is continuing under the senior indenture, then, and in each such case, either the trustee or the holders of not less than 25% in aggregate principal amount of such series then outstanding under the senior indenture (each such series voting as a separate class) by written notice to us and to the trustee, if such notice is given by the holders, may, and the trustee at the request of such holders shall, declare the principal amount of and accrued interest on such series of senior debt securities to be immediately due and payable, and upon this declaration, the same shall become immediately due and payable.

If an event of default specified in the fourth bullet point above occurs and is continuing, the entire principal amount of and accrued interest on each series of senior debt securities then outstanding shall automatically become immediately due and payable.

Unless otherwise specified in the prospectus supplement relating to a series of senior debt securities originally issued at a discount, the amount due upon acceleration shall include only the original issue price of the senior debt securities, the amount of original issue discount accrued to the date of acceleration and accrued interest, if any.

Upon certain conditions, declarations of acceleration may be rescinded and annulled and past defaults may be waived by the holders of a majority in aggregate principal amount of all the senior debt securities of such series affected by the default, each series voting as a separate class. Furthermore, subject to various provisions in the senior indenture, the holders of a majority in aggregate principal amount of a series of senior debt securities, by notice to the trustee, may waive a continuing default or event of default with respect to such senior debt

Table of Contents

securities and its consequences, except a default in the payment of principal of or interest on such senior debt securities (other than any such default in payment resulting solely from an acceleration of the senior debt securities) or in respect of a covenant or provision of the senior indenture which cannot be modified or amended without the consent of the holders of each such senior debt security. Upon any such waiver, such default shall cease to exist, and any event of default with respect to such senior debt securities shall be deemed to have been cured, for every purpose of the senior indenture; but no such waiver shall extend to any subsequent or other default or event of default or impair any right consequent thereto.

The holders of a majority in aggregate principal amount of a series of senior debt securities may direct the time, method and place of conducting any proceeding for any remedy available to the trustee or exercising any trust or power conferred on the trustee with respect to such senior debt securities. However, the trustee may refuse to follow any direction that conflicts with law or the senior indenture, that may involve the trustee in personal liability or that the trustee determines in good faith may be unduly prejudicial to the rights of holders of such series of senior debt securities not joining in the giving of such direction and may take any other action it deems proper that is not inconsistent with any such direction received from holders of such series of senior debt securities. A holder may not pursue any remedy with respect to the senior indenture or any series of senior debt securities unless:

the holder gives the trustee written notice of a continuing event of default;

the holders of at least 25% in aggregate principal amount of such series of senior debt securities make a written request to the trustee to pursue the remedy in respect of such event of default;

the requesting holder or holders offer the trustee indemnity satisfactory to the trustee against any costs, liability or expense;

the trustee does not comply with the request within 60 days after receipt of the request and the offer of indemnity; and

during such 60-day period, the holders of a majority in aggregate principal amount of such series of senior debt securities do not give the trustee a direction that is inconsistent with the request.

These limitations, however, do not apply to the right of any holder of a senior debt security of any affected series to receive payment of the principal of and interest on such senior debt security in accordance with the terms of such debt security, or to bring suit for the enforcement of any such payment in accordance with the terms of such debt security, on or after the due date for the senior debt securities, which right shall not be impaired or affected without the consent of the holder.

The senior indenture requires certain of our officers to certify, on or before a fixed date in each year in which any senior debt security is outstanding, as to their knowledge of our compliance with all covenants, agreements and conditions under the senior indenture.

Satisfaction and discharge. We can satisfy and discharge our obligations to holders of any series of debt securities if:

we have paid or caused to be paid the principal of and interest on all senior debt securities of such series (with certain limited exceptions) when due and payable; or

we deliver to the senior trustee for cancellation all senior debt securities of such series theretofore authenticated under the senior indenture (with certain limited exceptions); or

all senior debt securities of such series have become due and payable or will become due and payable within one year (or are to be called for redemption within one year under arrangements satisfactory to the senior

Table of Contents

trustee) and we deposit in trust an amount of cash or a combination of cash and U.S. government or U.S. government agency obligations (or in the case of senior debt securities denominated in a foreign currency, foreign government securities or foreign government agency securities) sufficient to make interest, principal and any other payments on the debt securities of that series on their various due dates; and if, in any such case, we also pay or cause to be paid all other sums payable under the senior indenture, as and when the same shall be due and payable and we deliver to the senior trustee an officer's certificate and an opinion of counsel, each stating that these conditions have been satisfied.

Under current U.S. federal income tax law, the deposit and our legal release from the debt securities would be treated as though we took back your debt securities and gave you your share of the cash and debt securities or bonds deposited in trust. In that event, you could recognize gain or loss on the debt securities you give back to us. Purchasers of the debt securities should consult their own advisers with respect to the tax consequences to them of such deposit and discharge, including the applicability and effect of tax laws other than the U.S. federal income tax law.

Defeasance. Unless the applicable prospectus supplement provides otherwise, the following discussion of legal defeasance and covenant defeasance will apply to any series of debt securities issued under the indentures.

Legal defeasance. We can legally release ourselves from any payment or other obligations on the debt securities of any series (called legal defeasance) if certain conditions are met, including the following:

We deposit in trust for your benefit and the benefit of all other direct holders of the debt securities of the same series cash or a combination of cash and U.S. government or U.S. government agency obligations (or, in the case of senior debt securities denominated in a foreign currency, foreign government or foreign government agency obligations) that will generate enough cash to make interest, principal and any other payments on the debt securities of that series on their various due dates.

There is a change in current U.S. federal income tax law or an IRS ruling that lets us make the above deposit without causing you to be taxed on the debt securities any differently than if we did not make the deposit and instead repaid the debt securities ourselves when due. Under current U.S. federal income tax law, the deposit and our legal release from the debt securities would be treated as though we took back your debt securities and gave you your share of the cash and debt securities or bonds deposited in trust. In that event, you could recognize gain or loss on the debt securities you give back to us.

We deliver to the trustee a legal opinion of our counsel confirming the tax law change or ruling described above. If we accomplish legal defeasance, as described above, you would have to rely solely on the trust deposit for repayment of the debt securities. You could not look to us for repayment in the event of any shortfall.

Covenant defeasance. Without any change in current U.S. federal tax law, we can make the same type of deposit described above and be released from some of the covenants in the debt securities (called covenant defeasance). In that event, you would lose the protection of those covenants but would gain the protection of having money and securities set aside in trust to repay the debt securities. In order to achieve covenant defeasance, we must do the following (among other things):

We must deposit in trust for your benefit and the benefit of all other direct holders of the debt securities of the same series cash or a combination of cash and U.S. government or U.S. government agency obligations (or, in the case of senior debt securities denominated in a foreign currency, foreign government or foreign government agency obligations) that will generate enough cash to make interest, principal and any other payments on the debt securities of that series on their various due dates.

Table of Contents

We must deliver to the trustee a legal opinion of our counsel confirming that under current U.S. federal income tax law we may make the above deposit without causing you to be taxed on the debt securities any differently than if we did not make the deposit and instead repaid the debt securities ourselves when due.

If we accomplish covenant defeasance, you could still look to us for repayment of the debt securities if there were a shortfall in the trust deposit. In fact, if one of the events of default occurred (such as our bankruptcy) and the debt securities become immediately due and payable, there may be such a shortfall. Depending on the events causing the default, you may not be able to obtain payment of the shortfall.

Modification and waiver. We and the trustee may amend or supplement the senior indenture or the senior debt securities of any series without the consent of any holder:

to convey, transfer, assign, mortgage or pledge any assets as security for the senior debt securities of one or more series;

to evidence the succession of a corporation, limited liability company, partnership or trust to us, and the assumption by such successor of our covenants, agreements and obligations under the senior indenture or to otherwise comply with the covenant relating to mergers, consolidations and sales of assets;

to comply with requirements of the SEC in order to effect or maintain the qualification of the senior indenture under the Trust Indenture Act of 1939, as amended (the Trust Indenture Act);

to add to our covenants such new covenants, restrictions, conditions or provisions for the protection of the holders, and to make the occurrence, or the occurrence and continuance, of a default in any such additional covenants, restrictions, conditions or provisions an event of default;

to cure any ambiguity, defect or inconsistency in the senior indenture or in any supplemental indenture or to conform the senior indenture or the senior debt securities to the description of senior debt securities of such series set forth in this prospectus or any applicable prospectus supplement;

to provide for or add guarantors with respect to the senior debt securities of any series;

to establish the form or forms or terms of the senior debt securities as permitted by the senior indenture;

to evidence and provide for the acceptance of appointment under the senior indenture by a successor trustee, or to make such changes as shall be necessary to provide for or facilitate the administration of the trusts in the senior indenture by more than one trustee;

to add to, change or eliminate any of the provisions of the senior indenture in respect of one or more series of senior debt securities, provided that any such addition, change or elimination shall (a) neither (1) apply to any senior debt security of any series created prior to the execution of such supplemental indenture and entitled to the benefit of such provision nor (2) modify the rights of the holder of any such senior debt security with respect to such provision or (b) become effective only when there is no senior debt security described in clause (a)(1) outstanding;

to make any change to the senior debt securities of any series so long as no senior debt securities of such series are outstanding; or

Edgar Filing: Karyopharm Therapeutics Inc. - Form 424B5

to make any change that does not adversely affect the rights of any holder in any material respect. Other amendments and modifications of the senior indenture or the senior debt securities issued may be made, and our compliance with any provision of the senior indenture with respect to any series of senior debt securities may be waived, with the consent of the holders of a majority of the aggregate principal amount of the outstanding senior debt securities of each series affected by the amendment or modification (voting as

Table of Contents

separate series); provided, however, that each affected holder must consent to any modification, amendment or waiver that:

extends the final maturity of any senior debt securities of such series;

reduces the principal amount of any senior debt securities of such series;

reduces the rate, or extends the time for payment of, interest on any senior debt securities of such series;

reduces the amount payable upon the redemption of any senior debt securities of such series;

changes the currency of payment of principal of or interest on any senior debt securities of such series;

reduces the principal amount of original issue discount securities payable upon acceleration of maturity or the amount provable in bankruptcy;

waives a continuing default in the payment of principal of or interest on the senior debt securities (other than any such default in payment resulting solely from an acceleration of the senior debt securities);

changes the provisions relating to the waiver of past defaults or impairs the right of holders to receive payment or to institute suit for the enforcement of any payment or conversion of any senior debt securities of such series on or after the due date therefor;

modifies any of the provisions of these restrictions on amendments and modifications, except to increase any required percentage or to provide that certain other provisions cannot be modified or waived without the consent of the holder of each senior debt security of such series affected by the modification;

adversely affects the right to convert or exchange senior debt securities into common stock or other property in accordance with the terms of the senior debt securities; or

reduces the above-stated percentage of outstanding senior debt securities of such series whose holders must consent to a supplemental indenture or modifies or amends or waives certain provisions of or defaults under the senior indenture.

It shall not be necessary for the holders to approve the particular form of any proposed amendment, supplement or waiver, but it shall be sufficient if the holders' consent approves the substance thereof. After an amendment, supplement or waiver of the senior indenture in accordance with the provisions described in this section becomes effective, the trustee must give to the holders affected thereby certain notice briefly describing the amendment, supplement or waiver. Any failure by the trustee to give such notice, or any defect therein, shall not, however, in any way impair or affect the validity of any such amendment, supplemental indenture or waiver.

No personal liability of incorporators, stockholders, officers, directors. The senior indenture provides that no recourse shall be had under any obligation, covenant or agreement of ours in the senior indenture or any supplemental indenture, or in any of the senior debt securities or because of the creation of any indebtedness represented thereby, against any of our incorporators, stockholders, officers or directors, past, present or future, or of any predecessor or successor entity thereof under any law, statute or constitutional provision or by the enforcement of any assessment or by any legal or equitable proceeding or otherwise. Each holder, by accepting the senior debt securities, waives and releases all

such liability.

Concerning the trustee. The senior indenture provides that, except during the continuance of an event of default, the trustee will not be liable except for the performance of such duties as are specifically set forth in the senior indenture. If an event of default has occurred and is continuing, the trustee will exercise such rights and powers vested in it under the senior indenture and will use the same degree of care and skill in its exercise as a prudent person would exercise under the circumstances in the conduct of such person's own affairs.

Table of Contents

The senior indenture and the provisions of the Trust Indenture Act incorporated by reference therein contain limitations on the rights of the trustee thereunder, should it become a creditor of ours or any of our subsidiaries, to obtain payment of claims in certain cases or to realize on certain property received by it in respect of any such claims, as security or otherwise. The trustee is permitted to engage in other transactions, provided that if it acquires any conflicting interest (as defined in the Trust Indenture Act), it must eliminate such conflict or resign.

We may have normal banking relationships with the senior trustee in the ordinary course of business.

Unclaimed funds. All funds deposited with the trustee or any paying agent for the payment of principal, premium, interest or additional amounts in respect of the senior debt securities that remain unclaimed for two years after the date upon which such amounts became due and payable will be repaid to us. Thereafter, any right of any holder of senior debt securities to such funds shall be enforceable only against us, and the trustee and paying agents will have no liability therefor.

Governing law. The senior indenture and the senior debt securities will be governed by, and construed in accordance with, the internal laws of the State of New York.

Certain terms of the subordinated debt securities

Other than the terms of the subordinated indenture and subordinated debt securities relating to subordination or otherwise as described in the prospectus supplement relating to a particular series of subordinated debt securities, the terms of the subordinated indenture and subordinated debt securities are identical in all material respects to the terms of the senior indenture and senior debt securities.

Additional or different subordination terms may be specified in the prospectus supplement applicable to a particular series.

Subordination. The indebtedness evidenced by the subordinated debt securities is subordinate to the prior payment in full of all of our senior indebtedness, as defined in the subordinated indenture. During the continuance beyond any applicable grace period of any default in the payment of principal, premium, interest or any other payment due on any of our senior indebtedness, we may not make any payment of principal of or interest on the subordinated debt securities (except for certain sinking fund payments). In addition, upon any payment or distribution of our assets upon any dissolution, winding-up, liquidation or reorganization, the payment of the principal of and interest on the subordinated debt securities will be subordinated to the extent provided in the subordinated indenture in right of payment to the prior payment in full of all our senior indebtedness. Because of this subordination, if we dissolve or otherwise liquidate, holders of our subordinated debt securities may receive less, ratably, than holders of our senior indebtedness. The subordination provisions do not prevent the occurrence of an event of default under the subordinated indenture.

The term *senior indebtedness* of a person means with respect to such person the principal of, premium, if any, interest on, and any other payment due pursuant to any of the following, whether outstanding on the date of the subordinated indenture or incurred by that person in the future:

all of the indebtedness of that person for money borrowed;

all of the indebtedness of that person evidenced by notes, debentures, bonds or other securities sold by that person for money;

all of the lease obligations that are capitalized on the books of that person in accordance with generally accepted accounting principles;

Table of Contents

all indebtedness of others of the kinds described in the first two bullet points above and all lease obligations of others of the kind described in the third bullet point above that the person, in any manner, assumes or guarantees or that the person in effect guarantees through an agreement to purchase, whether that agreement is contingent or otherwise; and

all renewals, extensions or refundings of indebtedness of the kinds described in the first, second or fourth bullet point above and all renewals or extensions of leases of the kinds described in the third or fourth bullet point above;
unless, in the case of any particular indebtedness, renewal, extension or refunding, the instrument creating or evidencing it or the assumption or guarantee relating to it expressly provides that such indebtedness, renewal, extension or refunding is not superior in right of payment to the subordinated debt securities. Our senior debt securities constitute senior indebtedness for purposes of the subordinated indenture.

Table of Contents

Description of capital stock

The following description of our capital stock is intended as a summary only and therefore is not a complete description of our capital stock. This description is based upon, and is qualified by reference to, our certificate of incorporation, our by-laws and applicable provisions of Delaware corporate law. You should read our certificate of incorporation and by-laws, which are filed as exhibits to the registration statement of which this prospectus forms a part, for the provisions that are important to you.

Our authorized capital stock consists of 100,000,000 shares of common stock, par value \$0.0001 per share, and 5,000,000 shares of preferred stock, par value \$0.0001 per share. As of December 31, 2017, 49,533,150 shares of common stock were outstanding and no shares of preferred stock were outstanding.

Common stock

Annual Meeting. Annual meetings of our stockholders are held on the date designated in accordance with our by-laws. Written notice must be mailed to each stockholder entitled to vote not less than ten nor more than 60 days before the date of the meeting. The presence in person or by proxy of the holders of record of a majority of our issued and outstanding shares entitled to vote at such meeting constitutes a quorum for the transaction of business at meetings of the stockholders. Special meetings of the stockholders may be called for any purpose by the board of directors, the chairman of the board or the chief executive officer. Except as may be otherwise provided by applicable law, our certificate of incorporation or our by-laws, all elections shall be decided by a plurality, and all other questions shall be decided by a majority, of the votes cast by stockholders entitled to vote thereon at a duly held meeting of stockholders at which a quorum is present.

Voting rights. Each holder of common stock is entitled to one vote for each share held on all matters to be voted upon by stockholders.

Dividends. Subject to the rights, powers and preferences of any outstanding preferred stock, and except as provided by law or in our certificate of incorporation, dividends may be declared and paid or set aside for payment on the common stock out of legally available assets or funds when and as declared by the board of directors.

Liquidation and dissolution. Subject to the rights, powers and preferences of any outstanding preferred stock, in the event of our liquidation or dissolution, our net assets will be distributed pro rata to the holders of our common stock.

Other rights. Holders of the common stock have no right to:

convert the stock into any other security;

have the stock redeemed;

purchase additional stock; or

maintain their proportionate ownership interest.

The common stock does not have cumulative voting rights. Holders of shares of the common stock are not required to make additional capital contributions.

Transfer agent and registrar. Computershare Trust Company, N.A., is transfer agent and registrar for the common stock.

Table of Contents

Preferred stock

We are authorized to issue blank check preferred stock, which may be issued in one or more series upon authorization of our board of directors. Our board of directors is authorized to fix the designations, powers, preferences and the relative, participating, optional or other special rights and any qualifications, limitations and restrictions of the shares of each series of preferred stock. The authorized shares of our preferred stock are available for issuance without further action by our stockholders, unless such action is required by applicable law or the rules of any stock exchange on which our securities may be listed. If the approval of our stockholders is not required for the issuance of shares of our preferred stock, our board may determine not to seek stockholder approval. The specific terms of any series of preferred stock offered pursuant to this prospectus will be described in the prospectus supplement relating to that series of preferred stock.

A series of our preferred stock could, depending on the terms of such series, impede the completion of a merger, tender offer or other takeover attempt. Our board of directors will make any determination to issue preferred shares based upon its judgment as to the best interests of our stockholders. Our directors, in so acting, could issue preferred stock having terms that could discourage an acquisition attempt through which an acquirer may be able to change the composition of our board of directors, including a tender offer or other transaction that some, or a majority, of our stockholders might believe to be in their best interests or in which stockholders might receive a premium for their stock over the then-current market price of the stock.

The preferred stock has the terms described below unless otherwise provided in the prospectus supplement relating to a particular series of preferred stock. You should read the prospectus supplement relating to the particular series of preferred stock being offered for specific terms, including:

the designation and stated value per share of the preferred stock and the number of shares offered;

the amount of liquidation preference per share;

the price at which the preferred stock will be issued;

the dividend rate, or method of calculation of dividends, the dates on which dividends will be payable, whether dividends will be cumulative or noncumulative and, if cumulative, the dates from which dividends will commence to accumulate;

any redemption or sinking fund provisions;

if other than the currency of the United States, the currency or currencies including composite currencies in which the preferred stock is denominated and/or in which payments will or may be payable;

any conversion provisions; and

any other rights, preferences, privileges, limitations and restrictions on the preferred stock.

The preferred stock will, when issued, be fully paid and non-assessable. Unless otherwise specified in the prospectus supplement, each series of preferred stock will rank equally as to dividends and liquidation rights in all respects with each other series of preferred stock. The rights of holders of shares of each series of preferred stock will be subordinate to those of our general creditors.

Rank. Unless otherwise specified in the prospectus supplement, the preferred stock will, with respect to dividend rights and rights upon our liquidation, dissolution or winding up of our affairs, rank:

senior to our common stock and to all equity securities ranking junior to such preferred stock with respect to dividend rights or rights upon our liquidation, dissolution or winding up of our affairs;

Table of Contents

on a parity with all equity securities issued by us, the terms of which specifically provide that such equity securities rank on a parity with the preferred stock with respect to dividend rights or rights upon our liquidation, dissolution or winding up of our affairs; and

junior to all equity securities issued by us, the terms of which specifically provide that such equity securities rank senior to the preferred stock with respect to dividend rights or rights upon our liquidation, dissolution or winding up of our affairs.

The term "equity securities" does not include convertible debt securities.

Dividends. Holders of the preferred stock of each series will be entitled to receive, when, as and if declared by our board of directors, cash dividends at such rates and on such dates described in the prospectus supplement. Different series of preferred stock may be entitled to dividends at different rates or based on different methods of calculation. The dividend rate may be fixed or variable or both. Dividends will be payable to the holders of record as they appear on our stock books on record dates fixed by our board of directors, as specified in the applicable prospectus supplement.

Dividends on any series of preferred stock may be cumulative or noncumulative, as described in the applicable prospectus supplement. If our board of directors does not declare a dividend payable on a dividend payment date on any series of noncumulative preferred stock, then the holders of that noncumulative preferred stock will have no right to receive a dividend for that dividend payment date, and we will have no obligation to pay the dividend accrued for that period, whether or not dividends on that series are declared payable on any future dividend payment dates. Dividends on any series of cumulative preferred stock will accrue from the date we initially issue shares of such series or such other date specified in the applicable prospectus supplement.

No dividends may be declared or paid or funds set apart for the payment of any dividends on any parity securities unless full dividends have been paid or set apart for payment on the preferred stock. If full dividends are not paid, the preferred stock will share dividends pro rata with the parity securities.

No dividends may be declared or paid or funds set apart for the payment of dividends on any junior securities unless full dividends for all dividend periods terminating on or prior to the date of the declaration or payment will have been paid or declared and a sum sufficient for the payment set apart for payment on the preferred stock.

Liquidation preference. Upon any voluntary or involuntary liquidation, dissolution or winding up of our affairs, then, before we make any distribution or payment to the holders of any common stock or any other class or series of our capital stock ranking junior to the preferred stock in the distribution of assets upon any liquidation, dissolution or winding up of our affairs, the holders of each series of preferred stock shall be entitled to receive out of assets legally available for distribution to stockholders, liquidating distributions in the amount of the liquidation preference per share set forth in the prospectus supplement, plus any accrued and unpaid dividends thereon. Such dividends will not include any accumulation in respect of unpaid noncumulative dividends for prior dividend periods. Unless otherwise specified in the prospectus supplement, after payment of the full amount of their liquidating distributions, the holders of preferred stock will have no right or claim to any of our remaining assets. Upon any such voluntary or involuntary liquidation, dissolution or winding up, if our available assets are insufficient to pay the amount of the liquidating distributions on all outstanding preferred stock and the corresponding amounts payable on all other classes or series of our capital stock ranking on parity with the preferred stock and all other such classes or series of shares of capital stock ranking on parity with the preferred stock in the distribution of assets, then the holders of the preferred stock and all other such classes or series of capital stock will share ratably in any such distribution of assets in proportion to the full liquidating distributions to which they would otherwise be entitled.

Table of Contents

Upon any such liquidation, dissolution or winding up and if we have made liquidating distributions in full to all holders of preferred stock, we will distribute our remaining assets among the holders of any other classes or series of capital stock ranking junior to the preferred stock according to their respective rights and preferences and, in each case, according to their respective number of shares. For such purposes, our consolidation or merger with or into any other corporation, trust or entity, or the sale, lease or conveyance of all or substantially all of our property or assets will not be deemed to constitute a liquidation, dissolution or winding up of our affairs.

Redemption. If so provided in the applicable prospectus supplement, the preferred stock will be subject to mandatory redemption or redemption at our option, as a whole or in part, in each case upon the terms, at the times and at the redemption prices set forth in such prospectus supplement.

The prospectus supplement relating to a series of preferred stock that is subject to mandatory redemption will specify the number of shares of preferred stock that shall be redeemed by us in each year commencing after a date to be specified, at a redemption price per share to be specified, together with an amount equal to all accrued and unpaid dividends thereon to the date of redemption. Unless the shares have a cumulative dividend, such accrued dividends will not include any accumulation in respect of unpaid dividends for prior dividend periods. We may pay the redemption price in cash or other property, as specified in the applicable prospectus supplement. If the redemption price for preferred stock of any series is payable only from the net proceeds of the issuance of shares of our capital stock, the terms of such preferred stock may provide that, if no such shares of our capital stock shall have been issued or to the extent the net proceeds from any issuance are insufficient to pay in full the aggregate redemption price then due, such preferred stock shall automatically and mandatorily be converted into the applicable shares of our capital stock pursuant to conversion provisions specified in the applicable prospectus supplement. Notwithstanding the foregoing, we will not redeem any preferred stock of a series unless:

if that series of preferred stock has a cumulative dividend, we have declared and paid or contemporaneously declare and pay or set aside funds to pay full cumulative dividends on the preferred stock for all past dividend periods and the then current dividend period; or

if such series of preferred stock does not have a cumulative dividend, we have declared and paid or contemporaneously declare and pay or set aside funds to pay full dividends for the then current dividend period.

In addition, we will not acquire any preferred stock of a series unless:

if that series of preferred stock has a cumulative dividend, we have declared and paid or contemporaneously declare and pay or set aside funds to pay full cumulative dividends on all outstanding shares of such series of preferred stock for all past dividend periods and the then current dividend period; or

if that series of preferred stock does not have a cumulative dividend, we have declared and paid or contemporaneously declare and pay or set aside funds to pay full dividends on the preferred stock of such series for the then current dividend period.

However, at any time we may purchase or acquire preferred stock of that series (1) pursuant to a purchase or exchange offer made on the same terms to holders of all outstanding preferred stock of such series or (2) by conversion into or exchange for shares of our capital stock ranking junior to the preferred stock of such series as to dividends and upon liquidation.

If fewer than all of the outstanding shares of preferred stock of any series are to be redeemed, we will determine the number of shares that may be redeemed pro rata from the holders of record of such shares in

Table of Contents

proportion to the number of such shares held or for which redemption is requested by such holder or by any other equitable manner that we determine. Such determination will reflect adjustments to avoid redemption of fractional shares.

Unless otherwise specified in the prospectus supplement, we will mail notice of redemption at least 30 days but not more than 60 days before the redemption date to each holder of record of preferred stock to be redeemed at the address shown on our stock transfer books. Each notice shall state:

the redemption date;

the number of shares and series of preferred stock to be redeemed;

the redemption price;

the place or places where certificates for such preferred stock are to be surrendered for payment of the redemption price;

that dividends on the shares to be redeemed will cease to accrue on such redemption date;

the date on which the holder's conversion rights, if any, as to such shares shall terminate; and

the specific number of shares to be redeemed from each such holder if fewer than all the shares of any series are to be redeemed.

If notice of redemption has been given and we have set aside the funds necessary for such redemption in trust for the benefit of the holders of any shares called for redemption, then from and after the redemption date, dividends will cease to accrue on such shares, and all rights of the holders of such shares will terminate, except the right to receive the redemption price.

Voting rights. Holders of preferred stock will not have any voting rights, except as required by law or as indicated in the applicable prospectus supplement.

Unless otherwise provided for under the terms of any series of preferred stock, no consent or vote of the holders of shares of preferred stock or any series thereof shall be required for any amendment to our certificate of incorporation that would increase the number of authorized shares of preferred stock or the number of authorized shares of any series thereof or decrease the number of authorized shares of preferred stock or the number of authorized shares of any series thereof (but not below the number of authorized shares of preferred stock or such series, as the case may be, then outstanding).

Conversion rights. The terms and conditions, if any, upon which any series of preferred stock is convertible into our common stock will be set forth in the applicable prospectus supplement relating thereto. Such terms will include the number of shares of common stock into which the shares of preferred stock are convertible, the conversion price, rate or manner of calculation thereof, the conversion period, provisions as to whether conversion will be at our option or at the option of the holders of the preferred stock, the events requiring an adjustment of the conversion price and provisions affecting conversion in the event of the redemption.

Transfer agent and registrar. The transfer agent and registrar for the preferred stock will be set forth in the applicable prospectus supplement.

Provisions of our certificate of incorporation and by-laws and Delaware law that may have anti-takeover effects

Edgar Filing: Karyopharm Therapeutics Inc. - Form 424B5

Board of directors. Our certificate of incorporation and by-laws provide for a board of directors divided as nearly equally as possible into three classes. Each class is elected to a term expiring at the annual meeting of

Table of Contents

stockholders held in the third year following the year of such election. The number of directors comprising our board of directors is fixed from time to time by the board of directors.

Removal of directors by stockholders. Our certificate of incorporation and by-laws provide that, subject to the rights of holders of any series of preferred stock, a member of our board of directors may only be removed for cause and only by an affirmative vote of the holders of at least 75% of the outstanding shares entitled to vote on the election of the directors.

Super-majority voting. The General Corporation Law of the State of Delaware, which we refer to as the DGCL, provides generally that the affirmative vote of a majority of the shares entitled to vote on any matter is required to amend a corporation's certificate of incorporation or by-laws, unless a corporation's certificate of incorporation or by-laws, as the case may be, requires a greater percentage. Subject to the rights of holders of any series of preferred stock, our by-laws may be amended or repealed by a majority vote of our board of directors or the affirmative vote of the holders of at least 75% of the votes that all our stockholders would be entitled to cast in any annual election of directors. In addition, the affirmative vote of the holders of at least 75% of the votes that all our stockholders would be entitled to cast in any annual election of directors is required to amend or repeal, or to adopt any provisions inconsistent with, any of the provisions of our certificate of incorporation described under the prior two paragraphs.

Stockholder nomination of directors. Our by-laws provide that a stockholder must notify us in writing of any stockholder nomination of a director not earlier than 120 days but not later than 90 days prior to the first anniversary of the preceding year's annual meeting; provided, that if the date of the annual meeting is advanced by more than 20 days, or delayed by more than 60 days, from such anniversary date, notice by the stockholder to be timely must be so delivered not earlier than the 120th day prior to the date of such annual meeting and not later than close of business on the later of (x) the 90th day prior to the date of such meeting and (y) the 10th day following the day on which notice of the date of such annual meeting was mailed or public announcement of the date of such annual meeting is first made by us, whichever occurs first.

No action by written consent. Our certificate of incorporation and our by-laws provide that our stockholders may not act by written consent and may only act at duly called meetings of stockholders. Our certificate of incorporation and our by-laws also provide that, except as otherwise required by law, special meetings of our stockholders can only be called by our board of directors, chairman of the board or chief executive officer. In addition, our by-laws establish an advance notice procedure for stockholder proposals to be brought before an annual meeting of stockholders, including proposed nominations of candidates for election to our board of directors.

Delaware business combination statute. We are subject to Section 203 of the DGCL. Subject to certain exceptions, Section 203 prevents a publicly held Delaware corporation from engaging in a business combination with any interested stockholder for three years following the date that the person became an interested stockholder, unless the interested stockholder attained such status with the approval of the corporation's board of directors or unless the business combination is approved in a prescribed manner or the interested stockholder acquired at least 85% of the corporation's outstanding voting stock in the transaction in which it became an interested stockholder. A business combination includes, among other things, a merger or consolidation involving us and the interested stockholder and the sale of more than 10% of our assets. In general, an interested stockholder is any entity or person beneficially owning 15% or more of our outstanding voting stock and any entity or person affiliated with or controlling or controlled by such entity or person.

Registration rights

We have entered into a third amended and restated investors' rights agreement, dated July 26, 2013, which we refer to as the investor rights agreement, with the former holders of shares of our preferred stock. Holders of a

Table of Contents

total of approximately 11.7 million shares of our common stock as of September 30, 2017 have the right to require us to register these shares under the Securities Act, and to participate in future registrations of securities by us, under the circumstances described below. After registration pursuant to these rights, these shares will become freely tradable without restriction under the Securities Act except that affiliates will need to comply with resale restrictions under Rule 144 of the Securities Act. If not otherwise exercised, the rights described below will expire five years after the closing of our initial public offering.

Demand registration rights

Subject to specified limitations set forth in the investor rights agreement, at any time, the holders of 50% or more of the then outstanding shares having rights under the investor rights agreement, which we refer to as registrable shares, may at any time demand in writing that we register all or a portion of the registrable shares under the Securities Act if the total amount of registrable shares registered have an anticipated aggregate offering price of at least \$5,000,000. We are not obligated to file a registration statement pursuant to this provision on more than two occasions.

In addition, subject to specified limitations set forth in the investor rights agreement, at any time after we become eligible to file a registration statement on Form S-3, holders of registrable shares outstanding may demand that we register on Form S-3 the registrable shares held by them so long as the total amount of registrable shares being registered has an aggregate offering price of at least \$1,000,000. We are not obligated to file a registration statement pursuant to this provision on more than two occasions in any 12-month period.

Incidental registration rights

If we propose to file a registration statement to register any of our securities under the Securities Act, either for our own account or for the account of any of our stockholders, other than pursuant to the demand registration rights described above and other than pursuant to a Form S-4 or Form S-8, the holders of our registrable shares are entitled to notice of registration and, subject to specified limitations set forth in the investor rights agreement, we will be required to use best efforts to register the registrable shares then held by them that they request that we register.

In the event that any registration in which the holders of registrable shares participate pursuant to our investor rights agreement is an underwritten public offering, we agree to enter into an underwriting agreement containing customary representations and warranties and covenants.

In the event that any registration in which the holders of registrable shares participate pursuant to our investor rights agreement is an underwritten public offering, we will use our best efforts to include the requested registrable shares to be included, but may be limited by market conditions.

Expenses

Pursuant to the investor rights agreement, we are required to pay all registration, qualification and filing fees, printing and accounting expenses, fees and expenses of one counsel to represent the selling stockholders and other reasonable direct costs for the selling stockholders (such selling stockholder expenses not to exceed \$50,000), but excluding underwriting discounts, selling commissions and the fees and expenses of selling stockholders' own counsel (other than the counsel selected to represent all selling stockholders). We are not required to pay registration expenses if the registration request under the investor rights agreement is withdrawn at the request of holders of a majority of the registrable shares, unless such holders agree to forfeit their right to one demand registration, or the withdrawal is due to discovery of a materially adverse change in our business.

Table of Contents

The investor rights agreement contains customary cross-indemnification provisions, pursuant to which we are obligated to indemnify the selling stockholders 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.

Table of Contents

Description of warrants

We may issue warrants to purchase common stock, preferred stock or debt securities. We may offer warrants separately or together with one or more additional warrants, common stock, preferred stock or debt securities, or any combination of those securities in the form of units, as described in the applicable prospectus supplement. If we issue warrants as part of a unit, the accompanying prospectus supplement will specify whether those warrants may be separated from the other securities in the unit prior to the expiration date of the warrants. The applicable prospectus supplement will also describe the following terms of any warrants:

the specific designation and aggregate number of, and the offering price at which we will issue, the warrants;

the currency or currency units in which the offering price, if any, and the exercise price are payable;

the date on which the right to exercise the warrants will begin and the date on which that right will expire or, if you may not continuously exercise the warrants throughout that period, the specific date or dates on which you may exercise the warrants;

whether the warrants are to be sold separately or with other securities as parts of units;

whether the warrants will be issued in definitive or global form or in any combination of these forms, although, in any case, the form of a warrant included in a unit will correspond to the form of the unit and of any security included in that unit;

any applicable material U.S. federal income tax consequences;

the identity of the warrant agent for the warrants and of any other depositaries, execution or paying agents, transfer agents, registrars or other agents;

the proposed listing, if any, of the warrants or any securities purchasable upon exercise of the warrants on any securities exchange;

the designation and terms of any equity securities purchasable upon exercise of the warrants;

the designation, aggregate principal amount, currency and terms of any debt securities that may be purchased upon exercise of the warrants;

if applicable, the designation and terms of the preferred stock with which the warrants are issued and the number of warrants issued with each security;

if applicable, the date from and after which any warrants issued as part of a unit and the related debt securities, preferred stock or common stock will be separately transferable;

Edgar Filing: Karyopharm Therapeutics Inc. - Form 424B5

the number of shares of common stock or preferred stock purchasable upon exercise of a warrant and the price at which those shares may be purchased;

if applicable, the minimum or maximum amount of the warrants that may be exercised at any one time;

information with respect to book-entry procedures, if any;

the anti-dilution provisions of, and other provisions for changes to or adjustment in the exercise price of, the warrants, if any;

any redemption or call provisions; and

any additional terms of the warrants, including terms, procedures and limitations relating to the exchange or exercise of the warrants.

Table of Contents

Description of units

We may issue units consisting of one or more of the other securities described in this prospectus in any combination, as described in the applicable prospectus supplement. We may issue units in one or more series, which will be described in the applicable prospectus supplement. The applicable prospectus supplement will also describe the following terms of any units:

the designation and the terms of the units and of the securities constituting the units, including whether and under what circumstances the securities comprising the units may be traded separately;

the identity of the unit agent for the units and of any other depositaries, execution or paying agents, transfer agents, registrars or other agents;

any additional terms of the governing unit agreement;

any additional provisions for the issuance, payment, settlement, transfer or exchange of the units or of the debt securities, common stock, preferred stock or warrants constituting the units; and

any applicable material U.S. federal income tax consequences.

Table of Contents

Forms of securities

Each debt security and warrant will be represented either by a certificate issued in definitive form to a particular investor or by one or more global securities representing the entire issuance of securities. Unless the applicable prospectus supplement provides otherwise, certificated securities will be issued in definitive form and global securities will be issued in registered form. Definitive securities name you or your nominee as the owner of the security, and in order to transfer or exchange these securities or to receive payments other than interest or other interim payments, you or your nominee must physically deliver the securities to the trustee, registrar, paying agent or other agent, as applicable. Global securities name a depository or its nominee as the owner of the debt securities or warrants represented by these global securities. The depository maintains a computerized system that will reflect each investor's beneficial ownership of the securities through an account maintained by the investor with its broker/dealer, bank, trust company or other representative, as we explain more fully below.

Global securities

We may issue the debt securities and warrants in the form of one or more fully registered global securities that will be deposited with a depository or its nominee identified in the applicable prospectus supplement and registered in the name of that depository or nominee. In those cases, one or more global securities will be issued in a denomination or aggregate denominations equal to the portion of the aggregate principal or face amount of the securities to be represented by global securities. Unless and until it is exchanged in whole for securities in definitive registered form, a global security may not be transferred except as a whole by and among the depository for the global security, the nominees of the depository or any successors of the depository or those nominees.

If not described below, any specific terms of the depository arrangement with respect to any securities to be represented by a global security will be described in the prospectus supplement relating to those securities. We anticipate that the following provisions will apply to all depository arrangements.

Ownership of beneficial interests in a global security will be limited to persons, called participants, that have accounts with the depository or persons that may hold interests through participants. Upon the issuance of a global security, the depository will credit, on its book-entry registration and transfer system, the participants' accounts with the respective principal or face amounts of the securities beneficially owned by the participants. Any dealers, underwriters or agents participating in the distribution of the securities will designate the accounts to be credited. Ownership of beneficial interests in a global security will be shown on, and the transfer of ownership interests will be effected only through, records maintained by the depository, with respect to interests of participants, and on the records of participants, with respect to interests of persons holding through participants. The laws of some states may require that some purchasers of securities take physical delivery of these securities in definitive form. These laws may impair your ability to own, transfer or pledge beneficial interests in global securities.

So long as the depository, or its nominee, is the registered owner of a global security, that depository or its nominee, as the case may be, will be considered the sole owner or holder of the securities represented by the global security for all purposes under the applicable indenture or warrant agreement. Except as described below, owners of beneficial interests in a global security will not be entitled to have the securities represented by the global security registered in their names, will not receive or be entitled to receive physical delivery of the securities in definitive form and will not be considered the owners or holders of the securities under the applicable indenture or warrant agreement. Accordingly, each person owning a beneficial interest in a global security must rely on the procedures of the depository for that global security and, if that person is not a

Table of Contents

participant, on the procedures of the participant through which the person owns its interest, to exercise any rights of a holder under the applicable indenture or warrant agreement. We understand that under existing industry practices, if we request any action of holders or if an owner of a beneficial interest in a global security desires to give or take any action that a holder is entitled to give or take under the applicable indenture or warrant agreement, the depositary for the global security would authorize the participants holding the relevant beneficial interests to give or take that action, and the participants would authorize beneficial owners owning through them to give or take that action or would otherwise act upon the instructions of beneficial owners holding through them.

Principal, premium, if any, and interest payments on debt securities, and any payments to holders with respect to warrants represented by a global security registered in the name of a depositary or its nominee will be made to the depositary or its nominee, as the case may be, as the registered owner of the global security. None of us, or any trustee, warrant agent, unit agent or other agent of ours, or any agent of any trustee, warrant agent or unit agent will have any responsibility or liability for any aspect of the records relating to payments made on account of beneficial ownership interests in the global security or for maintaining, supervising or reviewing any records relating to those beneficial ownership interests.

We expect that the depositary for any of the securities represented by a global security, upon receipt of any payment to holders of principal, premium, interest or other distribution of underlying securities or other property on that registered global security, will immediately credit participants' accounts in amounts proportionate to their respective beneficial interests in that global security as shown on the records of the depositary. We also expect that payments by participants to owners of beneficial interests in a global security held through participants will be governed by standing customer instructions and customary practices, as is now the case with the securities held for the accounts of customers or registered in street name, and will be the responsibility of those participants.

If the depositary for any of the securities represented by a global security is at any time unwilling or unable to continue as depositary or ceases to be a clearing agency registered under the Exchange Act, and a successor depositary registered as a clearing agency under the Exchange Act is not appointed by us within 90 days, we will issue securities in definitive form in exchange for the global security that had been held by the depositary. Any securities issued in definitive form in exchange for a global security will be registered in the name or names that the depositary gives to the relevant trustee, warrant agent, unit agent or other relevant agent of ours or theirs. It is expected that the depositary's instructions will be based upon directions received by the depositary from participants with respect to ownership of beneficial interests in the global security that had been held by the depositary.

Table of Contents

Plan of distribution

We may sell securities:

- through underwriters;
- through dealers;
- through agents;
- directly to purchasers; or
- through a combination of any of these methods of sale.

In addition, we may issue the securities as a dividend or distribution or in a subscription rights offering to our existing security holders. This prospectus may be used in connection with any offering of our securities through any of these methods or other methods described in the applicable prospectus supplement.

We may directly solicit offers to purchase securities, or agents may be designated to solicit such offers. We will, in the prospectus supplement relating to such offering, name any agent that could be viewed as an underwriter under the Securities Act, and describe any commissions that we must pay. Any such agent will be acting on a best efforts basis for the period of its appointment or, if indicated in the applicable prospectus supplement, on a firm commitment basis.

The distribution of the securities may be effected from time to time in one or more transactions:

- at a fixed price, or prices, which may be changed from time to time;
- at market prices prevailing at the time of sale;
- at prices related to such prevailing market prices; or
- at negotiated prices.

Each prospectus supplement will describe the method of distribution of the securities and any applicable restrictions.

The prospectus supplement with respect to the securities of a particular series will describe the terms of the offering of the securities, including the following:

- the name of the agent or any underwriters;
- the public offering or purchase price and the proceeds we will receive from the sale of the securities;
- any discounts and commissions to be allowed or re-allowed or paid to the agent or underwriters;
- all other items constituting underwriting compensation;
- any discounts and commissions to be allowed or re-allowed or paid to dealers; and
- any exchanges on which the securities will be listed.

If any underwriters or agents are utilized in the sale of the securities in respect of which this prospectus is delivered, we will enter into an underwriting agreement or other agreement with them at the time of sale to them, and we will set forth in the prospectus supplement relating to such offering the names of the underwriters or agents and the terms of the related agreement with them.

If a dealer is utilized in the sale of the securities in respect of which this prospectus is delivered, we will sell such securities to the dealer, as principal. The dealer may then resell such securities to the public at varying prices to be determined by such dealer at the time of resale.

If we offer securities in a subscription rights offering to our existing security holders, we may enter into a standby underwriting agreement with dealers, acting as standby underwriters. We may pay the standby underwriters a commitment fee for the securities they commit to purchase on a standby basis. If we do not enter into a standby underwriting arrangement, we may retain a dealer-manager to manage a subscription rights offering for us.

Table of Contents

Remarketing firms, agents, underwriters, dealers and other persons may be entitled under agreements which they may enter into with us to indemnification by us against certain civil liabilities, including liabilities under the Securities Act, and may be customers of, engage in transactions with or perform services for us in the ordinary course of business.

If so indicated in the applicable prospectus supplement, we will authorize underwriters or other persons acting as our agents to solicit offers by certain institutions to purchase securities from us pursuant to delayed delivery contracts providing for payment and delivery on the date stated in the prospectus supplement. Each contract will be for an amount not less than, and the aggregate amount of securities sold pursuant to such contracts shall not be less nor more than, the respective amounts stated in the prospectus supplement. Institutions with whom the contracts, when authorized, may be made include commercial and savings banks, insurance companies, pension funds, investment companies, educational and charitable institutions and other institutions, but shall in all cases be subject to our approval. Delayed delivery contracts will not be subject to any conditions except that:

the purchase by an institution of the securities covered under that contract shall not at the time of delivery be prohibited under the laws of the jurisdiction to which that institution is subject; and

if the securities are also being sold to underwriters acting as principals for their own account, the underwriters shall have purchased such securities not sold for delayed delivery. The underwriters and other persons acting as our agents will not have any responsibility in respect of the validity or performance of delayed delivery contracts.

Certain agents, underwriters and dealers, and their associates and affiliates may be customers of, have borrowing relationships with, engage in other transactions with, and/or perform services, including investment banking services, for us or one or more of our respective affiliates in the ordinary course of business.

In order to facilitate the offering of the securities, any underwriters may engage in transactions that stabilize, maintain or otherwise affect the price of the securities or any other securities the prices of which may be used to determine payments on such securities. Specifically, any underwriters may overallocate in connection with the offering, creating a short position for their own accounts. In addition, to cover overallocations or to stabilize the price of the securities or of any such other securities, the underwriters may bid for, and purchase, the securities or any such other securities in the open market. Finally, in any offering of the securities through a syndicate of underwriters, the underwriting syndicate may reclaim selling concessions allowed to an underwriter or a dealer for distributing the securities in the offering if the syndicate repurchases previously distributed securities in transactions to cover syndicate short positions, in stabilization transactions or otherwise. Any of these activities may stabilize or maintain the market price of the securities above independent market levels. Any such underwriters are not required to engage in these activities and may end any of these activities at any time.

Under Rule 15c6-1 of the Exchange Act, trades in the secondary market generally are required to settle in two business days, unless the parties to any such trade expressly agree otherwise or the securities are sold by us to an underwriter in a firm commitment underwritten offering. The applicable prospectus supplement may provide that the original issue date for your securities may be more than two scheduled business days after the trade date for your securities. Accordingly, in such a case, if you wish to trade securities on any date prior to the second business day before the original issue date for your securities, you will be required, by virtue of the fact that your securities initially are expected to settle in more than two scheduled business days after the trade date for your securities, to make alternative settlement arrangements to prevent a failed settlement.

The securities may be new issues of securities and may have no established trading market. The securities may or may not be listed on a national securities exchange. We can make no assurance as to the liquidity of or the existence of trading markets for any of the securities.

Table of Contents

Legal matters

Unless the applicable prospectus supplement indicates otherwise, the validity of the securities in respect of which this prospectus is being delivered will be passed upon by Wilmer Cutler Pickering Hale and Dorr LLP.

Experts

The consolidated financial statements of Karyopharm Therapeutics Inc. appearing in Karyopharm Therapeutics Inc.'s Annual Report (Form 10-K) as of and for the years ended December 31, 2016 and 2015 have been audited by Ernst & Young LLP, independent registered public accounting firm, as set forth in their report thereon, included therein, and incorporated herein by reference. Such consolidated financial statements are incorporated herein by reference in reliance upon such report given on the authority of such firm as experts in accounting and auditing.

Table of Contents

\$125,000,000

Common stock

Preliminary prospectus supplement

J.P. Morgan

Jefferies

Leerink Partners

Canaccord Genuity JMP Securities H.C. Wainwright & Co. Baird

May , 2018