Filed Pursuant to Rule 424(b)(5)
Registration No. 333-232283

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 we are not soliciting offers to buy these securities in any jurisdiction where the offer or sale is not permitted.

SUBJECT TO COMPLETION, DATED FEBRUARY 4, 2020

PRELIMINARY PROSPECTUS SUPPLEMENT
(To Prospectus dated June 21, 2019)

Shares

ZIOPHARM Oncology, Inc.

Common Stock

We are offering shares of our common stock. Our common stock is listed on The Nasdaq Global Select Market under the symbol "ZIOP." On February 3, 2020, the last reported sale price of our common stock was $4.00 per share.

Investing in our common stock involves a high degree of risk. Please read "Risk Factors" beginning on page S-7 of this prospectus supplement, on page 9 of the accompanying prospectus and in the documents incorporated by reference into this prospectus supplement and the accompanying prospectus.

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

	PER SHARE	TOTAL
Public offering price	$	$
Underwriting discounts and commissions (1)	$	$
Proceeds to Ziopharm, before expenses	$	$

(1) See "Underwriting" beginning on page S-13 of this prospectus supplement for additional information regarding the compensation payable to the underwriter.

We have granted the underwriters an option for a period of 30 days to purchase up to an additional shares of common stock from us at the public offering price, less the underwriting discounts and commissions. 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 $.

The underwriters expect to deliver the shares of common stock to investors on or about , 2020.

Sole Book-Running Manager

Jefferies

Lead Manager

Cantor

The date of this prospectus supplement is , 2020.

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ABOUT THIS PROSPECTUS SUPPLEMENT

This prospectus supplement and the accompanying prospectus are part of an automatic shelf registration statement on Form S-3 (File No. 333-232283) that we filed with the Securities and Exchange Commission, or SEC, on June 21, 2019 as a "well-known seasoned issuer", as defined in Rule 405 under the Securities Act of 1933, as amended, or the Securities Act, using a "shelf" registration process. Under this shelf registration process, we may sell shares of our common stock, preferred stock, debt securities and warrants under the prospectus from time to time at prices and on terms to be determined by market conditions at the time of the offering described in the accompanying prospectus.

This document is in two parts. The first part is this prospectus supplement, which describes the specific terms of this offering and also adds to and updates information contained in the accompanying prospectus and the documents incorporated by reference herein and therein. The second part, the accompanying prospectus, provides more general information, some of which may not apply to this offering. Generally, when we refer to this prospectus, we are referring to this prospectus supplement and the accompanying prospectus 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 herein or 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 specified in the relevant agreement. Accordingly, such representations, warranties and covenants should not be relied on as accurately representing the current state of our affairs.

You should rely only on the information contained in or incorporated by reference in this prospectus supplement, the accompanying prospectus and in any free writing prospectus that we have authorized for use in connection with this offering. We have not, and the underwriter has not, authorized anyone to provide you with different information. If anyone provides you with different or inconsistent information, you should not rely on it. We are not, and the underwriter is not, making an offer to sell these securities in any jurisdiction where the offer or sale is not permitted. You should assume that the information in this prospectus supplement, the accompanying prospectus, the documents incorporated by reference herein and therein, and in any free writing prospectus that we have authorized for use in connection with this common stock offering, is accurate only as of the date of those respective documents. Our business, financial condition, results of operations and prospects may have changed since those dates. You should read this prospectus supplement, the accompanying prospectus, the documents incorporated by reference herein and therein, and any free writing prospectus that we have authorized for use in connection with this offering, in their entirety before making an investment decision. You should also read and consider the additional information in the documents to which we have referred you in the sections of this prospectus supplement and in the accompanying prospectus entitled "Where You Can Find More Information" and "Incorporation of Information by Reference."

We and the underwriter 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. This prospectus supplement and the accompanying prospectus do not constitute, and may not be used in connection with, an offer to sell, or a solicitation of an offer to buy, any securities offered by this prospectus supplement and the

accompanying prospectus by any person in any jurisdiction in which it is unlawful for such person to make such an offer or solicitation.

Unless otherwise stated, all references in this prospectus supplement and the accompanying prospectus to “we,” “us,” “our,” “Ziopharm,” the “Company” and similar designations refer to Ziopharm Oncology, Inc.

This prospectus supplement and the accompanying prospectus contains references to our trademarks and to trademarks belonging to other entities. Solely for convenience, trademarks and trade names referred to in this prospectus supplement and the accompanying prospectus, including logos, artwork and other visual displays, may appear without the ® or ™ symbols, but such references are not intended to indicate, in any way, that their respective owners will not assert, to the fullest extent under applicable law, their rights thereto. We do not intend our use or display of other companies’ trade names or trademarks to imply a relationship with, or endorsement or sponsorship of us by, any other companies.

PROSPECTUS SUPPLEMENT SUMMARY

This summary highlights certain information about us, this offering and selected information contained elsewhere in or incorporated by reference in this prospectus supplement. This summary is not complete and does not contain all of the information that you should consider before deciding whether to invest in our common stock. For a more complete understanding of our company and this offering, we encourage you to read and consider carefully the more detailed information in this prospectus supplement and the accompanying prospectus, including the information referred to under the heading "Risk Factors" in this prospectus supplement beginning on page S-7, the information referred to under the heading "Risk Factors" in the accompanying prospectus beginning on page 9, the information incorporated by reference in this prospectus supplement and the accompanying prospectus, which are described under "Where You Can Find More Information" and "Incorporation of Information by Reference," and the information included in any free writing prospectus that we have authorized for use in connection with this offering.

Company Overview

We are a clinical-stage biopharmaceutical company focused on discovering, acquiring, developing and commercializing next generation immunotherapy platforms that leverage cell- and gene-based therapies to treat patients with cancer. We are developing two immuno-oncology platform technologies that utilize the immune system by employing novel, controlled gene expression and innovative cell engineering technologies designed to deliver safe, effective, and scalable non-viral cell- and viral-based gene therapies for the treatment of multiple cancer types. Our first platform is referred to as *Sleeping Beauty* and is based on the genetic engineering of immune cells using a non-viral transposon/transposase system that is intended to stably reprogram T cells outside of the body for subsequent infusion. Our second platform is termed Controlled IL-12, which is designed to stimulate expression of interleukin 12, or IL-12, a master regulator of the immune system, in a controlled and safe manner to focus the patient's immune system to attack cancer cells. We believe these two platforms have the potential to provide unique and powerful solutions to address the issues associated with (1) treating solid tumors with heterogeneous and unknown antigens, and (2) providing cost-effective scalable manufacturing solutions for T cell receptor T cell, or TCR+ T, therapies for solid tumors and chimeric antigen receptor, or CAR T cell, or CAR+ T, therapies targeting CD19 on malignant B cells.

Using our *Sleeping Beauty* platform, we are developing TCR+ T therapies initially to target solid tumors. Our T cell receptor, or TCR, program designs and manufactures T cells that are intended to target tumor-specific antigens, thereby delivering personalized therapy that can attack an individual patient's cancer. These antigens are referred to as neoantigens as they are only expressed by the tumor, reducing the potential for toxicity upon targeting normal cells. A minority of neoantigens are shared between patients and between classes of tumors and are referred to as "hotspots". The *Sleeping Beauty* system uses DNA plasmids to reprogram T cells to express introduced TCRs on a patient-by-patient basis (addressing inter-tumor heterogeneity) and possibly to express more than one TCR for each patient (addressing intra-tumor heterogeneity). The genetic modification using the *Sleeping Beauty* system of recipient-derived products enables us to target neoantigens in two ways. The first recognizes that most neoantigens are unique to each patient's tumor and we plan to infuse TCR+ T cells expressing recipient-derived (autologous) TCRs. The second is based on the finding that some neoantigens in hotspots are shared between patients and we plan to administer TCR+ T expressing allogeneic TCRs from a library derived from third parties. We have in-licensed from the National Cancer Institute, or the NCI, multiple allogeneic TCRs derived from third parties that are reactive to mutated KRAS, TP53 and EGFR and we plan to expand our TCR library as part of our commitment to advance clinical development for the treatment of patients whose solid tumors have driver mutations. These TCRs are typically obtained from tumor-infiltrating lymphocytes, or TILs.

Under our Cooperative Research and Development Agreement, the NCI is conducting a Phase 2 clinical trial to evaluate autologous peripheral blood lymphocytes genetically modified with the *Sleeping Beauty* system to

express autologous (personalized) TCRs. The U.S. Food and Drug Administration, or FDA, has cleared the investigational new drug, or IND, application submitted by the NCI for this clinical trial. The trial was initiated in October 2019 and preparations to enable patient enrollment by the NCI are underway. We expect the trial will enroll patients with a broad range of solid tumors over the next several years.

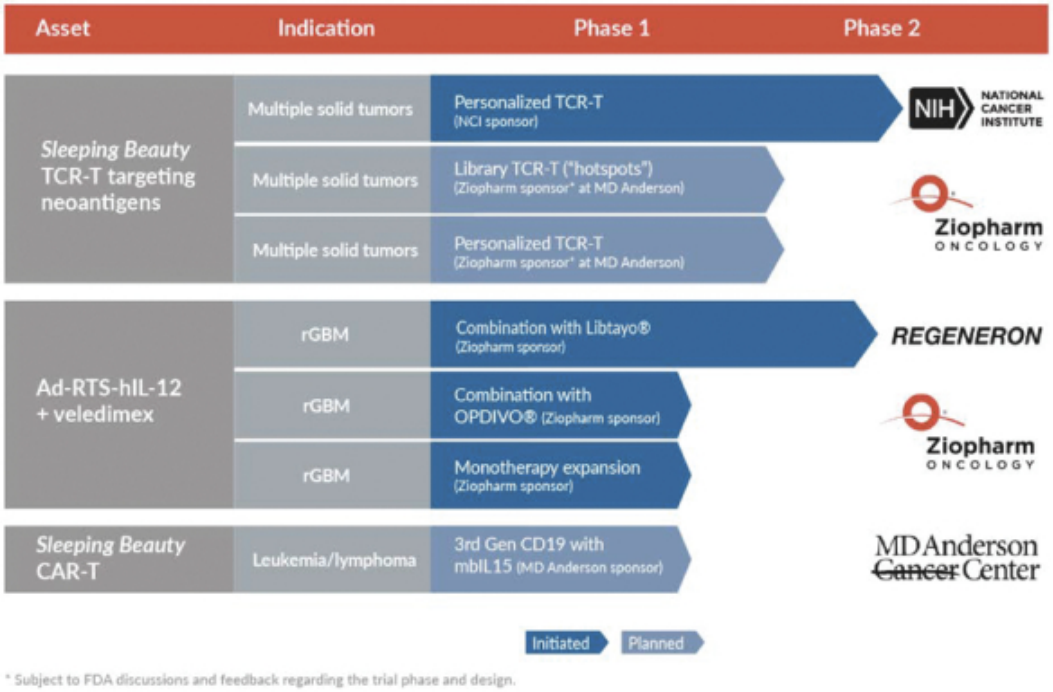
In addition, we are currently planning a clinical program to study our TCR approach with The University of Texas MD Anderson Cancer Center, or MD Anderson. Under this program, we expect to evaluate both our personalized TCR, or autoTCR, approach and our hotspot TCR, or alloTCR, approach. Our autoTCR approach is designed to identify neoantigens and TCRs on a patient-by-patient basis, which we believe should allow it to be broadly applicable to many patients' solid tumors. The advantage of the alloTCR approach is that a subset of patients with solid tumors may be rapidly treated based on screening them for target neoantigens (*e.g.*, in TP53), identifying human leukocyte antigen, and matching these data to the alloTCRs in the library.

We are also developing CAR+ T therapies using our *Sleeping Beauty* platform. Our CAR+ T program seeks to solve the complex and costly manufacturing limitations that we believe continue to limit the commercial potential of existing CD19-specific CAR+ T therapies. We believe using DNA plasmids in the *Sleeping Beauty* system to express a CD19-specific CAR and our proprietary membrane-bound interleukin 15, or mbIL15, in resting T cells obtained from peripheral blood will enable infused T cells to propagate within the patient to target leukemia and lymphoma, thus avoiding the need to numerically expand T cells for weeks in bioreactors before patient administration. The mbIL15 is co-expressed with a "kill switch" or "safety switch" to conditionally eliminate infused T cells. We expect the lower cost of DNA plasmids compared with the virus used by other CAR+ T programs, together with the avoidance of lengthy *ex vivo* manufacturing, will reduce the cost and complexity of manufacturing CAR+ T cells. These technologies should enable T cells to be infused as soon as the day after gene transfer in a process we refer to as rapid personalized manufacture, or RPM. We are advancing our CAR+ T technology in the United States in collaboration with MD Anderson in a Phase 1 clinical trial in the United States infusing CD19-specific CAR+ T therapies manufactured using our RPM technology. In this trial, we plan to infuse donor-derived T cells after allogeneic bone marrow transplantation, or BMT, for recipients who have relapsed with CD19+ leukemias and lymphomas. We are also advancing our RPM technology including using patient-derived (autologous) T cells in order to treat patients with relapsed or refractory CD19+ leukemias and lymphomas. In a joint venture with TriArm Therapeutics, Ltd., or TriArm, we have formed Eden BioCell, Ltd., or Eden BioCell, to lead the clinical development and commercialization of *Sleeping Beauty*-generated CD19-specific RPM CAR-T therapies in the People's Republic of China, Taiwan and Korea. Eden BioCell is focused on advancing our RPM technology using patient-derived (autologous) T cells in order to treat patients with relapsed or refractory CD19+ leukemias and lymphomas. Eden BioCell is owned equally by us and TriArm and the parties share decision-making authority. TriArm has committed up to $35.0 million, of which $10.0 million has been paid as of September 30, 2019, to this joint venture and will also manage all clinical development to execute trials in the designated countries.

Our Controlled IL-12 platform uses virotherapy based on an engineered replication-incompetent adenovirus, referred to as Ad-RTS-hIL-12, plus veledimex as a gene delivery system to conditionally produce IL-12, a potent, naturally occurring anti-cancer protein, to treat patients with solid tumors where a specific target is unknown, including brain cancer. Our Controlled IL-12 platform allows us to deliver IL-12 in a tunable dose as the cytokine is under transcriptional control of the rheoSwitch therapeutic system® (RTS®). We believe the ability regulate production of IL-12 after administration of the virus is critical for the development of this potent cytokine. We are currently studying our Controlled IL-12 Platform as a monotherapy in a Phase 1 clinical trial of patients with recurrent glioblastoma multiforme, or rGBM. Our substudy of this clinical trial is fully enrolled with 36 patients diagnosed with rGBM. The substudy is designed to encourage use of low-dose steroids and 20 mg veledimex to further understand the potential of Controlled IL-12 as a monotherapy. We are also developing our Controlled IL-12 platform in combination with immune checkpoint inhibitors. We are studying Ad-RTS-hIL-12 plus veledimex in combination with OPDIVO® (nivolumab) in a Phase 1 dose-escalation clinical trial of patients with rGBM. We have entered into a clinical supply agreement with Regeneron Pharmaceuticals, Inc., or Regeneron, to evaluate Ad-RTS-hIL-12 plus veledimex in

combination with Regeneron's PD-1antibody Libtayo® (cemiplimab-rwlc) for the treatment of patients with rGBM. We have initiated a Phase 2 clinical trial evaluating Controlled IL-12 (Ad-RTS-hIL-12 plus veledimex, Ad+V), in combination with PD-1 antibody Libtayo® (cemiplimab-rwlc) for the treatment of recurrent or progressive glioblastoma multiforme in adults. In our clinical trials, we have observed that Controlled IL-12 increases T-cell activity in the tumor microenvironment in patients with rGBM and we may conduct trials of Controlled IL-12 in other tumor types as both a monotherapy and in combination with immune checkpoint inhibitors.

Our Pipeline



Recent Developments

Sleeping Beauty Solid Tumor TCR-T Program

We expect to pursue our TCR+T cell therapy program in collaboration with MD Anderson. In October 2019, we entered into the 2019 Research and Development Agreement with MD Anderson where, we will, among other things, collaborate with MD Anderson on programs to expand our TCR library and conduct clinical trials.

As part of our effort to continue expanding our TCR library, in January 2020, we announced an amendment to our license with the NCI to expand our license to include additional TCRs reactive to mutated KRAS and TP53. We also announced in January 2020 that the journal *Clinical Cancer Research* published a paper, co-authored by Drew Deniger, Ph.D., who leads our TCR+T cell therapy program. The *Clinical Cancer Research* publication describes how TCRs with specificity to mutations within TP53 present in tumor cells can be obtained from circulating T cells, which may overcome the need to obtain TILs through surgical resection.

Our third generation CAR+ T program utilizes our proprietary mbIL15, which enables infused T cells to propagate within the patient, thus avoiding the need to numerically expand T cells for weeks in bioreactors before patient administration. At the American Society of Hematology, or ASH, Annual Meeting in December

2019, we presented pre-clinical data of our RPM technology demonstrating that T cells genetically modified using DNA plasmids from the *Sleeping Beauty* system to express TCRs with mbIL15 exhibit anti-tumor effects.

Controlled IL-12 Platform

In November 2019, we provided an update from two ongoing studies of our Controlled IL-12 platform at the 2019 Society for Neuro-Oncology, or SNO, Annual Meeting.

Monotherapy Expansion Substudy—Interim Results

In a Phase 1 clinical trial of patients with rGBM, referred to as the Main Study, a subset of patients (n=6) with unifocal disease who received single administration of Ad-RTS-hIL-12 with 20 mg daily dosing (15 total planned doses) of veledimex along with low-dose steroids along, achieved 17.8 months median overall survival, or mOS. Thirty-six additional patients with rGBM were recruited into a substudy, referred to as the Expansion Substudy, designed to encourage use of low-dose steroids and 20 mg veledimex to further understand the potential of Controlled IL-12 as a monotherapy. During the 2019 SNO Annual Meeting, we provided an interim update for the Expansion Substudy and announced that:

- We observed a decrease in tumor from baseline resulted in a patient's lesion being too small to measure, assessed as a partial response (per iRANO), with follow up ongoing.
- We provided an analysis of MRI findings of pseudoprogression in subjects with initial increases and subsequent decreases in tumor size, which was consistent with immune-mediated anti-tumor effects.
- We observed that subjects in the Expansion Substudy were comparable to the subjects in the Main Study, except a higher percentage of subjects enrolled in the Expansion Substudy had multifocal disease (as compared with unifocal disease) and fewer previous recurrences of disease.
- Subjects receiving 20 mg of veledimex in both the Main Study and Expansion Substudy (n=20) with unifocal disease at entry, receiving low-dose steroids (defined as <20 mg cumulative dosing of dexamethasone during the time of veledimex dosing) had a mOS of 16.2 months. The mOS for these subjects in the Expansion Substudy alone (n=14) has not been reached at a mean follow up of 9.7 months
- We observed subjects with multifocal disease at initial enrollment that received 20mg of veledimex and low-dose steroids (n=13) had a mOS of 10.1 months. We believe this is consistent with literature, which shows that multifocal glioblastoma is associated with worse prognosis compared to unifocal disease
- Adverse reactions that we observed in the Expansion Substudy as of the data cut-off date were consistent with prior studies of Controlled IL-12 and were predictable, dose-related, and promptly reversible upon discontinuation of veledimex

Combination Study—Interim Results

We are also studying Ad-RTS-hIL-12 plus veledimex in combination with nivolumab, an immune checkpoint inhibitor, in a Phase 1 dose-escalation trial of patients with rGBM. During the 2019 SNO Annual Meeting, we provided an interim update for this trial and announced that:

- We observed a decrease of approximately 64% in a patient's tumor from baseline resulting in a partial response (per iRANO), with follow up ongoing.
- We provided an analysis of MRI findings of pseudoprogression in subjects, which was consistent with immune-mediated anti-tumor effects.
- Active dosing is ongoing in the trial and mOS has not been reached, with a mean follow up for these subjects of 4.8 months.
- No dose limiting toxicities, no serious adverse events that were considered related to the combination with nivolumab and no clinically significant overlapping toxicities have been observed as of the data cut-off date in the trial.

- Drug-related toxicities we have observed as of the data cut-off date were comparable to the Main Study, and have been predictable, dose-related, and promptly reversible upon discontinuation of veledimex. Further, there were no drug-related deaths reported.

Sleeping Beauty Solid Tumor CAR+ T Program

In October 2019, we announced the FDA had cleared an IND application submitted by MD Anderson Cancer Center for a Phase 1 clinical trial to evaluate our third generation CD19-specific CAR-T therapies for patients with relapsed CD19+ leukemias and lymphomas. The clinical trial will evaluate CAR-T therapies prepared using our RPM technology.

In January 2020, we announced that a letter published in the *Blood*, the journal of the American Society of Hematology, discussed long-term outcomes of seven patients with relapsed or refractory B-cell lymphoid malignancies, all of whom had received our second-generation CD19-specific CAR-T cells infused two days following autologous hematopoietic stem-cell transplantation, also referred to as BMT. In this study, four of the seven patients demonstrated sustained persistence of CAR-T (median time of persistence duration was 4.5 years, range 2-5 years). Five-year progression-free survival and overall survival were 71% and 86%, respectively.

Financial Update

As of December 31, 2019, we had approximately $79.7 million of cash and cash equivalents. This amount is unaudited and preliminary, and does not present all information necessary for an understanding of our financial condition as of December 31, 2019. Our internal closing procedures with respect to the period presented above are not complete. In connection with the preparation of our financial statements for the year ended December 31, 2019, we identified a potential error in our accounting for expenses related to a clinical trial which started in late 2018. We are in the process of assessing this potential error including assessing any financial reporting implications, which may possibly result in an addition to our accrued expenses for this clinical trial, and assessing the impact, if any, on our internal controls. Based on our evaluation to date, we do not believe the potential error will be deemed material nor do we believe it will result in a restatement of our financial statements. Our actual results for the year ended December 31, 2019 will not be finalized until after this offering is completed and may differ materially from the above estimates.

Corporate Information

We originally incorporated in Colorado in September 1998 (under the name Net Escapes, Inc.) and later changed our name to “EasyWeb, Inc.” in February 1999. We re-incorporated in Delaware on May 16, 2005 under the same name. On September 13, 2005, we completed a “reverse” acquisition of privately held ZIOPHARM, Inc., a Delaware corporation. To effect this transaction, we caused ZIO Acquisition Corp., our wholly-owned subsidiary, to merge with and into ZIOPHARM, Inc., with ZIOPHARM, Inc. surviving as our wholly owned subsidiary. In accordance with the terms of the merger, the outstanding common stock of ZIOPHARM, Inc. automatically converted into the right to receive an aggregate of approximately 97.3% of our outstanding common stock (after giving effect to the transaction). Following the merger, we caused ZIOPHARM, Inc. to merge with and into us and we changed our name to “ZIOPHARM Oncology, Inc.” Although EasyWeb, Inc. was the legal acquirer in the transaction, we accounted for the transaction as a reverse acquisition under generally accepted accounting principles. As a result, ZIOPHARM, Inc. became the registrant with the Securities and Exchange Commission and the historical financial statements of ZIOPHARM, Inc. became our historical financial statements.

Our principal executive offices are located at One First Avenue, Parris Building 34, Navy Yard Plaza, Boston, Massachusetts 02129, and our telephone number is (617) 259-1970. Our website is www.ziopharm.com. Information found on, or accessible through, our website is not a part of, and is not incorporated into, this prospectus supplement or the accompanying prospectus, and you should not consider it part of this prospectus supplement or part of the accompanying prospectus.

THE OFFERING

Common stock offered by us in this offering	shares of our common stock
Option to purchase additional shares	We have granted the underwriters an option for a period of 30 days from the date of this prospectus supplement to purchase up to additional shares of common stock.
Common stock to be outstanding immediately after this offering	shares (or shares if the underwriters exercise in full their option to purchase additional shares).
Use of proceeds	We estimate that the net proceeds to us from this offering will be approximately $ million, or $ million if the underwriters exercise their option to purchase additional shares in full, in each case after deducting estimated underwriting discounts and commissions and estimated offering expenses payable by us. We intend to use the net proceeds from this offering for progressing our clinical programs towards commercialization, working capital and other general corporate purposes. See "Use of Proceeds."
Risk factors	You should read the "Risk Factors" section beginning on page S-7 of this prospectus supplement and in the documents incorporated by reference herein for a discussion of certain of the factors to consider carefully before deciding to purchase any shares of our common stock.
Nasdaq Global Select Market symbol	ZIOP

The number of shares of common stock to be outstanding immediately after this offering is based on 181,030,020 shares of common stock outstanding as of September 30, 2019 and excludes:

- 5,960,549 shares of our common stock issuable upon the exercise of stock options outstanding as of September 30, 2019, having a weighted average exercise price of $4.12 per share;
- 3,525,512 shares of our common stock available as of September 30, 2019 for future issuance pursuant to our 2012 Equity Incentive Plan; and
- 18,939,394 shares of our common stock issuable upon the exercise of warrants to purchase shares of our common stock outstanding as of September 30, 2019, at a weighted-average exercise price of $6.76 per share.

RISK FACTORS

An investment in our common stock involves a high degree of risk. Before deciding whether to invest in our common stock, you should consider carefully the risks described below and discussed under the section captioned "Risk Factors" contained in our Quarterly Report on Form 10-Q for the period ended September 30, 2019, which is incorporated by reference in this prospectus supplement and the accompanying prospectus, in its entirety, together with other information in this prospectus supplement, the accompanying prospectus, the information and documents incorporated by reference, and in any free writing prospectus that we have authorized for use in connection with this offering. See "Where You Can Find More Information" and "Incorporation of Certain Information by Reference." If any of these risks actually occurs, our business, financial condition, results of operations or cash flow could be harmed. This could cause the trading price of our common stock to decline, resulting in a loss of all or part of your investment. The risks described below and in the documents referenced above are not the only ones that we face. Additional risks not presently known to us or that we currently deem immaterial may also affect our business.

Risks Related to this Offering

We will require substantial additional financial resources to continue ongoing development of our product candidates and pursue our business objectives; if we are unable to obtain these additional resources when needed, we may be forced to delay or discontinue our planned operations, including clinical testing of our product candidates.

We have not generated significant revenue and have incurred significant net losses in each year since our inception. For the nine months ended September 30, 2019, we had a net loss of $102.1 million, and, as of September 30, 2019, we have incurred approximately $668.4 million of accumulated deficit since our inception in 2003. We expect to continue to incur significant operating expenditures and net losses. Further development of our product candidates will likely require substantial increases in our expenses as we:

- continue to undertake clinical trials for product candidates;
- scale-up the formulation and manufacturing of our product candidates;
- seek regulatory approvals for product candidates;
- work with regulatory authorities to identify and address program-related inquiries;
- implement additional internal systems and infrastructure; and
- hire additional personnel.

We continue to seek additional financial resources to fund the further development of our product candidates. If we are unable to obtain sufficient additional capital, one or more of these programs could be placed on hold.

As of September 30, 2019, we have approximately $88.4 million of cash and cash equivalents. Given our current development plans, we expect that our existing cash and cash equivalents will be sufficient to fund our current operations into the first half of 2021.

Management does not know whether additional financing will be available when needed on acceptable terms or at all. If adequate additional funds are not available when required, or if we are unsuccessful in entering into partnership agreements for further development of our product candidates, management may need to curtail its development efforts and planned operations.

Management will have broad discretion as to the use of the proceeds from this offering, and we may not use the proceeds effectively.

Our management will have broad discretion in the application of the net proceeds from this offering and could spend the proceeds in ways that do not improve our results of operations or enhance the value of our common stock. Accordingly, you will be relying on the judgment of our management with regard to the use of these net proceeds, and you will not have the opportunity, as part of your investment decision, to assess whether the proceeds are being used appropriately. It is possible that the proceeds will be used in a way that does not yield a favorable, or any, return for us. Our failure to apply these funds effectively could have a material adverse effect on our business, delay the development of our product candidates and cause the price of our common stock to decline.

Future sales of our common stock by us or our existing stockholders could cause the market price of our common stock to decline 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 such sales may occur, could reduce the market price of our common stock.

We, our executive officers and directors have entered into lock-up agreements with the underwriters under which we and they have agreed, subject to certain exceptions, not to sell, directly or indirectly, any shares of our common stock without the permission of the underwriters for a period of 90 days following the date of this prospectus supplement. We refer to such period as the lock-up period. When the lock-up period expires, we, our executive officers and directors will be able to sell shares of common stock in the public market, subject to compliance with applicable securities laws restrictions. In addition, the underwriters may, in their sole discretion, release all or some portion of the shares of common stock subject to lock-up agreements at any time and for any reason. Sales of a substantial number of such shares of common stock upon expiration of the lock-up or otherwise, the perception that such sales may occur, or early release of these agreements, could cause the market price of our common stock to fall or make it more difficult for you to sell your common stock at a time and price that you deem appropriate.

You may experience future dilution as a result of future equity offerings and other issuances of our common stock.

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. We cannot assure you that we will be able to sell shares or other securities in any other offering at a price per share that is equal to or greater 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, including investors who purchase shares of common stock in this offering. The price per share at which we sell additional shares of our common stock or securities convertible into common stock in future transactions may be higher or lower than the price per share in this offering.

Our stock price is volatile and may decline regardless of our operating performance, and you may not be able to resell your shares at or above the price at which you purchased such shares.

The market price for our common stock is volatile and may fluctuate significantly in response to a number of factors, most of which we cannot control, including:

- price and volume fluctuations in the overall stock market;
- market conditions or trends in our industry or the economy as a whole;
- changes in operating performance and stock market valuations of other biopharmaceutical companies generally, or those that develop and commercialize cancer drugs in particular;
- the financial or operational projections we may provide to the public, any changes in these projections or our failure to meet these projections;
- changes in financial estimates or ratings by any securities analysts who follow our common stock, our failure to meet these estimates or failure of those analysts to initiate or maintain coverage of our common stock;
- the public's response to press releases or other public announcements by us or third parties, including our filings with the SEC, and announcements relating to product development, litigation and intellectual property impacting us or our business;
- the sustainability of an active trading market for our common stock;
- future sales of our common stock by our executive officers, directors and significant stockholders;
- announcements of mergers or acquisition transactions;
- our inclusion or deletion from certain stock indices;
- announcements of medical innovations or new products by our competitors;
- announcements of changes in our senior management;
- other events or factors, including those resulting from war, incidents of terrorism, natural disasters or responses to these events; and
- changes in accounting principles.

In addition, the stock markets, and in particular the Nasdaq Global Select Market, have experienced extreme price and volume fluctuations that have affected and continue to affect the market prices of equity securities of many biopharmaceutical companies. Stock prices of many biopharmaceutical companies have fluctuated in a manner unrelated or disproportionate to the operating performance of those companies. In the past, stockholders have instituted securities class action litigation following periods of market volatility. If we were involved in securities litigation, we could incur substantial costs and our resources and the attention of management could be diverted from our business.

SPECIAL NOTE REGARDING FORWARD-LOOKING STATEMENTS

This prospectus supplement and the accompanying prospectus contain, and the documents incorporated by reference herein and therein and any free writing prospectus that we have authorized for use in connection with this offering may contain, forward-looking statements within the meaning of Section 27A of the Securities Act of 1933, as amended, and Section 21E of the Securities Exchange Act of 1934, as amended, or the Exchange Act. All statements other than statements of historical facts contained in this prospectus supplement, the accompanying prospectus and the information we incorporate by reference are forward-looking statements. These statements relate to future events or to our future operating or financial performance and involve known and unknown risks, uncertainties and other factors which may cause our actual results, performance or achievements to be materially different from any future results, performances or achievements expressed or implied by the forward-looking statements. Forward-looking statements may include, but are not limited to statements about:

In some cases, you can identify forward-looking statements by terms such “anticipate,” “believe,” “estimate,” “expect,” “forecast,” “intend,” “may,” “plan,” “project,” “target,” “will” and other words and terms of similar meaning. These statements reflect our current views with respect to future events and are based on assumptions and subject to risks and uncertainties. Given these uncertainties, you should not place undue reliance on these forward-looking statements. We discuss many of these risks in greater detail under the heading “Risk Factors” in this prospectus supplement and in our SEC filings.

You should read this prospectus supplement, the accompanying prospectus, the documents we have filed with the SEC that are incorporated by reference and any free writing prospectus that we have authorized for use in connection with this offering completely and with the understanding that our actual future results may be materially different from what we expect. We qualify all of the forward-looking statements in the foregoing documents by these cautionary statements. You should not place undue reliance on these statements. Forward-looking statements speak only as of the date of the document containing the applicable statement. We do not undertake any obligation to publicly update any forward-looking statements. Reference is made in particular to forward-looking statements regarding:

- our ability to raise substantial additional capital to fund our planned operations in the near term and to continue as a going concern;
- our estimates regarding expenses, use of cash, timing of future cash needs and capital requirements;
- the development of our product candidates, including statements regarding the timing of initiation, completion and the outcome of clinical studies or trials and related preparatory work and the period during which the results of the trials will become available;
- our ability to advance our product candidates through various stages of development, especially through pivotal safety and efficacy trials;
- the risk that final trial data may not support interim analysis of the viability of our product candidates;
- our expectations regarding the safety and efficacy of our product candidates, and the progress and timing of our research and development programs;
- the timing, scope or likelihood of regulatory filings and approvals from the U.S. Food and Drug Administration or equivalent foreign regulatory agencies for our product candidates and for which indications;
- our ability to license additional intellectual property relating to our product candidates from third parties and to comply with our existing license agreements;
- our ability to enter into partnerships or achieve the results contemplated by our collaboration agreements and the benefits to be derived from relationships with collaborators;
- developments and projections relating to competition from other pharmaceutical and biotechnology companies or our industry;
- our estimates regarding the potential market opportunity for our product candidates;
- the anticipated rate and degree of market acceptance of our product candidates for any indication, if approved;

- the anticipated amount, timing and accounting of contract liability (formerly deferred revenue), milestones and other payments under licensing, collaboration or acquisition agreements, research and development costs and other expenses;
- our intellectual property position, including the strength and enforceability of our intellectual property rights;
- our ability to attract and retain qualified employees and key personnel;
- the impact of government laws and regulations in the United States and foreign countries; and
- our estimates with respect to cash and cash equivalents for the year ended December 31, 2019; and
- other risks and uncertainties

USE OF PROCEEDS

We estimate that the net proceeds to us from this offering, after deducting the underwriting discounts and commissions and estimated offering expenses payable by us, will be approximately $ million (or approximately $ million if the underwriters exercise their option to purchase additional shares in full).

We currently intend to use the net proceeds from this offering for progressing our clinical programs towards commercialization, working capital and other general corporate purposes.

The amount and timing of these expenditures will depend on a number of factors, including the progress of our research and development efforts, the progress of any partnering efforts, technological advances and the competitive environment for our product candidates. Accordingly, you will be relying on the judgment of our management with regard to the use of these net proceeds, and you will not have the opportunity, as part of your investment decision, to assess whether the proceeds are being used appropriately. It is possible that the proceeds will be used in a way that does not yield a favorable, or any, return for us. Pending application of the net proceeds as described above, we intend to invest the proceeds in investment grade interest bearing instruments.

UNDERWRITING

Subject to the terms and conditions set forth in the underwriting agreement, dated February , 2020, between us and Jefferies LLC, as the representative of the underwriters named below and the sole book-running manager of this offering, we have agreed to sell to the underwriters, and each of the underwriters has agreed, severally and not jointly, to purchase from us, the respective number of shares of common stock shown opposite its name below:

UNDERWRITER	NUMBER OF SHARES
Jefferies LLC	
Cantor Fitzgerald & Co.	
Total	

The underwriting agreement provides that the obligations of the several underwriters are subject to certain conditions precedent such as the receipt by the underwriters of officers' certificates and legal opinions and approval of certain legal matters by their counsel. The underwriting agreement provides that the underwriters will purchase all of the shares of common stock if any of them are purchased. If an underwriter defaults, the underwriting agreement provides that the purchase commitments of the nondefaulting underwriters may be increased or the underwriting agreement may be terminated. We have agreed to indemnify the underwriters and certain of their controlling persons against certain liabilities, including liabilities under the Securities Act, and to contribute to payments that the underwriters may be required to make in respect of those liabilities.

The underwriters have advised us that, following the completion of this offering, they currently intend to make a market in the common stock as permitted by applicable laws and regulations. However, the underwriters are not obligated to do so, and the underwriters may discontinue any market-making activities at any time without notice in their sole discretion. Accordingly, no assurance can be given as to the liquidity of the trading market for the common stock, that you will be able to sell any of the common stock held by you at a particular time or that the prices that you receive when you sell will be favorable.

The underwriters are offering the shares of common stock subject to their acceptance of the shares of common stock from us and subject to prior sale. The underwriters reserve the right to withdraw, cancel or modify offers to the public and to reject orders in whole or in part.

Commission and Expenses

The following table shows the public offering price, the underwriting discounts and commissions that we are to pay the underwriters and the proceeds, before expenses, to us in connection with this offering. Such amounts are shown assuming both no exercise and full exercise of the underwriters' option to purchase additional shares.

	PER SHARE		TOTAL	
	WITHOUT OPTION TO PURCHASE ADDITIONAL SHARES	WITH OPTION TO PURCHASE ADDITIONAL SHARES	WITHOUT OPTION TO PURCHASE ADDITIONAL SHARES	WITH OPTION TO PURCHASE ADDITIONAL SHARES
Public offering price	$	$	$	$
Underwriting discounts and commissions paid by us	$	$	$	$
Proceeds to us, before expenses	$	$	$	$

We estimate expenses payable by us in connection with this offering, other than the underwriting discounts and commissions referred to above, will be approximately $.

Option to Purchase Additional Shares

We have granted to the underwriters an option, exercisable for 30 days from the date of this prospectus, to purchase, from time to time, in whole or in part, up to an aggregate of shares from us at the public offering price set

forth on the cover page of this prospectus, less underwriting discounts and commissions. If the underwriters exercise this option, each underwriter will be obligated, subject to specified conditions, to purchase a number of additional shares proportionate to that underwriter's initial purchase commitment as indicated in the table above.

No Sales of Similar Securities

Pursuant to certain "lock-up" agreements, we, our executive officers and our directors have agreed that for a period of 90 days following the pricing of the offering, and subject to certain exceptions, not to offer, sell, assign, transfer, pledge, contract to sell, or otherwise dispose of or announce the intention to otherwise dispose of, or enter into any swap, hedge or similar agreement or arrangement that transfers, in whole or in part, the economic consequence of ownership of, directly or indirectly, or make any demand or request or exercise any right with respect to the registration of, or file with the SEC a registration statement under the Securities Act relating to, any common stock or securities convertible into or exchangeable or exercisable for any common stock without the prior written consent of Jefferies LLC.

Stabilization

The underwriters have advised us that they, pursuant to Regulation M under the Securities Exchange Act of 1934, as amended, certain persons participating in the offering may engage in short sale transactions, stabilizing transactions, syndicate covering transactions or the imposition of penalty bids in connection with this offering. These activities may have the effect of stabilizing or maintaining the market price of the common stock at a level above that which might otherwise prevail in the open market. Establishing short sales positions may involve either "covered" short sales or "naked" short sales.

"Covered" short sales are sales made in an amount not greater than the underwriters' option to purchase additional shares of our common stock in this offering. The underwriters may close out any covered short position by either exercising their option to purchase additional shares of our common stock or purchasing shares of our common stock in the open market. In determining the source of shares to close out the covered short position, the underwriters will consider, among other things, the price of shares available for purchase in the open market as compared to the price at which they may purchase shares through the option to purchase additional shares.

"Naked" short sales are sales in excess of the option to purchase additional shares of our common stock. The underwriters must close out any naked short position by purchasing shares in the open market. 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 shares of our common stock in the open market after pricing that could adversely affect investors who purchase in this offering.

A stabilizing bid is a bid for the purchase of shares of common stock on behalf of the underwriters for the purpose of fixing or maintaining the price of the common stock. A syndicate covering transaction is the bid for or the purchase of shares of common stock on behalf of the underwriters to reduce a short position incurred by the underwriters in connection with the offering. Similar to other purchase transactions, the underwriter's purchases to cover the syndicate short sales may have the effect of raising or maintaining the market price of our common stock or preventing or retarding a decline in the market price of our common stock. As a result, the price of our common stock may be higher than the price that might otherwise exist in the open market. A penalty bid is an arrangement permitting the underwriters to reclaim the selling concession otherwise accruing to a syndicate member in connection with the offering if the common stock originally sold by such syndicate member are purchased in a syndicate covering transaction and therefore have not been effectively placed by such syndicate member.

Neither we nor any of the underwriters make any representation or prediction as to the direction or magnitude of any effect that the transactions described above may have on the price of our common stock. The underwriters are not obligated to engage in these activities and, if commenced, any of the activities may be discontinued at any time.

The underwriters may also engage in passive market making transactions in our common stock on The NASDAQ Global Select Market in accordance with Rule 103 of Regulation M during a period before the commencement of offers or sales of shares of our common stock in this offering and extending through the completion of distribution. A passive market maker must display its bid at a price not in excess of the highest independent bid of that security.

However, if all independent bids are lowered below the passive market maker's bid, that bid must then be lowered when specified purchase limits are exceeded.

Electronic Distribution

A prospectus in electronic format may be made available by e-mail or on the web sites or through online services maintained by one or more of the underwriters or their affiliates. In those cases, prospective investors may view offering terms online and may be allowed to place orders online. The underwriters may agree with us to allocate a specific number of shares of common stock for sale to online brokerage account holders. Any such allocation for online distributions will be made by the underwriters on the same basis as other allocations. Other than the prospectus in electronic format, the information on the underwriters' web sites and any information contained in any other web site maintained by any of the underwriters is not part of this prospectus, has not been approved and/or endorsed by us or the underwriters and should not be relied upon by investors.

Other Activities and Relationships

The underwriter and certain of its affiliates are full service financial institutions engaged in various activities, which may include securities trading, commercial and investment banking, financial advisory, investment management, investment research, principal investment, hedging, financing and brokerage activities. The underwriter and certain of its affiliates have, from time to time, performed, and may in the future perform, various commercial and investment banking and financial advisory services for us and our affiliates, for which they received or will receive customary fees and expenses.

In the ordinary course of their various business activities, the underwriter and certain of its affiliates may make or hold a broad array of investments and actively trade debt and equity securities (or related derivative securities) and financial instruments (including bank loans) for their own account and for the accounts of their customers, and such investment and securities activities may involve securities and/or instruments issued by us and our affiliates. If the underwriters or their respective affiliates have a lending relationship with us, they routinely hedge their credit exposure to us consistent with their customary risk management policies. The underwriters and their respective affiliates may hedge such exposure by entering into transactions which consist of either the purchase of credit default swaps or the creation of short positions in our securities or the securities of our affiliates, including potentially the common stock offered hereby. Any such short positions could adversely affect future trading prices of the common stock offered hereby. The underwriters and certain of their respective affiliates may also communicate independent investment recommendations, market color or trading ideas and/or publish or express independent research views in respect of such securities or instruments and may at any time hold, or recommend to clients that they acquire, long and/or short positions in such securities and instruments.

Disclaimers About Non-U.S. Jurisdictions

Canada

(A) Resale Restrictions

The distribution of shares of common stock in Canada is being made only in the provinces of Ontario, Quebec, Alberta and British Columbia on a private placement basis exempt from the requirement that we prepare and file a prospectus with the securities regulatory authorities in each province where trades of these securities are made. Any resale of the common stock in Canada must be made under applicable securities laws which may vary depending on the relevant jurisdiction, and which may require resales to be made under available statutory exemptions or under a discretionary exemption granted by the applicable Canadian securities regulatory authority. Purchasers are advised to seek legal advice prior to any resale of the securities.

(B) Representations of Canadian Purchasers

By purchasing common stock in Canada and accepting delivery of a purchase confirmation, a purchaser is representing to us and the dealer from whom the purchase confirmation is received that:

- the purchaser is entitled under applicable provincial securities laws to purchase the common stock without the benefit of a prospectus qualified under those securities laws as it is an "accredited investor" as defined under National Instrument 45-106—*Prospectus Exemptions*,

- the purchaser is a "permitted client" as defined in National Instrument 31-103—*Registration Requirements, Exemptions and Ongoing Registrant Obligations*,
- where required by law, the purchaser is purchasing as principal and not as agent, and
- the purchaser has reviewed the text above under Resale Restrictions.

(C) Conflicts of Interest

Canadian purchasers are hereby notified that Jefferies LLC is relying on the exemption set out in section 3A.3 or 3A.4, if applicable, of National Instrument 33-105 – *Underwriting Conflicts* from having to provide certain conflict of interest disclosure in this document.

(D) Statutory Rights of Action

Securities legislation in certain provinces or territories of Canada may provide a purchaser with remedies for rescission or damages if the offering memorandum (including any amendment thereto) such as this document 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 of these securities in Canada 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.

(E) Enforcement of Legal Rights

All of our directors and officers as well as the experts named herein may be located outside of Canada and, as a result, it may not be possible for Canadian purchasers to effect service of process within Canada upon us or those persons. All or a substantial portion of our assets and the assets of those persons may be located outside of Canada and, as a result, it may not be possible to satisfy a judgment against us or those persons in Canada or to enforce a judgment obtained in Canadian courts against us or those persons outside of Canada.

(F) Taxation and Eligibility for Investment

Canadian purchasers of common stock should consult their own legal and tax advisors with respect to the tax consequences of an investment in the common stock in their particular circumstances and about the eligibility of the common stock for investment by the purchaser under relevant Canadian legislation.

Australia

This Offering Memorandum is not a disclosure document for the purposes of Australia's Corporations Act 2001 (Cth) of Australia, or Corporations Act, has not been lodged with the Australian Securities & Investments Commission and is only directed to the categories of exempt persons set out below. Accordingly, if you receive this Offering Memorandum in Australia:

(A) You confirm and warrant that you are either:

- a "sophisticated investor" under section 708(8)(a) or (b) of the Corporations Act;
- a "sophisticated investor" under section 708(8)(c) or (d) of the Corporations Act and that you have provided an accountant's certificate to the Company which complies with the requirements of section 708(8)(c)(i) or (ii) of the Corporations Act and related regulations before the offer has been made;
- a person associated with the Company under Section 708(12) of the Corporations Act; or
- a "professional investor" within the meaning of section 708(11)(a) or (b) of the Corporations Act.

To the extent that you are unable to confirm or warrant that you are an exempt sophisticated investor, associated person or professional investor under the Corporations Act any offer made to you under this Offering Memorandum is void and incapable of acceptance.

(B) You warrant and agree that you will not offer any of the securities issued to you pursuant to this Offering Memorandum for resale in Australia within 12 months of those securities being issued unless any such resale offer is exempt from the requirement to issue a disclosure document under section 708 of the Corporations Act.

European Economic Area

In relation to each member state of the European Economic Area (each, an "EEA Member State"), an offer to the public of any securities which are the subject of the offering contemplated by this prospectus supplement and the accompanying prospectus may not be made in that EEA Member State except that an offer to the public in that EEA Member State of any securities may be made at any time under the following exemptions under the Prospectus Regulation:

(a) to any legal entity which is a "qualified investor" as defined in the Prospectus Regulation;

(b) to fewer than 150 natural or legal persons (other than qualified investors as defined in the Prospectus Regulation), as permitted under the Prospectus Regulation, subject to obtaining the prior consent of the underwriters or the underwriters nominated by us for any such offer; or

(c) in any other circumstances falling within Article 1(4) of the Prospectus Regulation,

provided that no such offer of securities shall require us or any of the underwriters to publish a prospectus pursuant to Article 3 of the Prospectus Regulation or supplement a prospectus pursuant to Article 23 of the Prospectus Regulation.

For the purposes of this provision, the expression "offer to the public" in relation to any securities in any EEA Member State means the communication in any form and by any means of sufficient information on the terms of the offer and the securities to be offered so as to enable an investor to decide to purchase or subscribe the securities, and the expression "Prospectus Regulation" means Regulation (EU) 2017/1129.

Hong Kong

No securities have been offered or sold, and no securities may be offered or sold, in Hong Kong, by means of any document, other than to persons whose ordinary business is to buy or sell shares or debentures, whether as principal or agent; or to "professional investors" as defined in the Securities and Futures Ordinance (Cap. 571) of Hong Kong ("SFO") and any rules made under that Ordinance; or in other circumstances which do not result in the document being a "prospectus" as defined in the Companies Ordinance (Cap. 32) of Hong Kong ("CO") or which do not constitute an offer or invitation to the public for the purpose of the CO or the SFO. No document, invitation or advertisement relating to the securities has been issued or may be issued or may be in the possession of any person for the purpose of issue (in each case 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 under the securities laws of Hong Kong) other than with respect to securities which are or are intended to be disposed of only to persons outside Hong Kong or only to "professional investors" as defined in the SFO and any rules made under that Ordinance.

This Offering Memorandum has not been registered with the Registrar of Companies in Hong Kong. Accordingly, this Offering Memorandum may not be issued, circulated or distributed in Hong Kong, and the securities may not be offered for subscription to members of the public in Hong Kong. Each person acquiring the securities will be required, and is deemed by the acquisition of the securities, to confirm that he is aware of the restriction on offers of the securities described in this Offering Memorandum and the relevant offering documents and that he is not acquiring, and has not been offered any securities in circumstances that contravene any such restrictions.

Israel

This document does not constitute a prospectus under the Israeli Securities Law, 5728-1968, or the Securities Law, and has not been filed with or approved by the Israel Securities Authority. In Israel, this prospectus is being distributed only to, and is directed only at, and any offer of the common stock is directed only at, (i) a limited number of persons in accordance with the Israeli Securities Law and (ii) investors listed in the first addendum, or the Addendum, to the Israeli Securities Law, consisting primarily of joint investment in trust funds, provident funds, insurance companies, banks, portfolio managers, investment advisors, members of the Tel Aviv Stock Exchange, underwriters, venture capital funds, entities with equity in excess of NIS 50 million and "qualified individuals," each as defined in the Addendum (as it may be amended from time to time), collectively referred to as qualified investors (in each case, purchasing for their own account or, where permitted under the Addendum, for the accounts of their clients who are investors listed in the Addendum). Qualified investors are required to submit written confirmation that they fall within the scope of the Addendum, are aware of the meaning of same and agree to it.

Japan

The offering has not been and will not be registered under the Financial Instruments and Exchange Law of Japan (Law No. 25 of 1948 of Japan, as amended), or FIEL, and the Initial Purchaser will not offer or sell any securities, 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, any resident of Japan, except pursuant to an exemption from the registration requirements of, and otherwise in compliance with, the FIEL and any other applicable laws, regulations and ministerial guidelines of Japan.

Singapore

This Offering Memorandum has not been and will not be lodged or registered as a prospectus with the Monetary Authority of Singapore. Accordingly, this Offering Memorandum and any other document or material in connection with the offer or sale, or invitation for subscription or purchase, of the notes may not be circulated or distributed, nor may the notes 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 (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 notes 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 notes pursuant to an offer made under Section 275 of the SFA except:

(i) 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;

(ii) where no consideration is or will be given for the transfer;

(iii) where the transfer is by operation of law;

(iv) as specified in Section 276(7) of the SFA; or

(v) as specified in Regulation 32 of the Securities and Futures (Offers of Investments) (Shares and Debentures) Regulations 2005 of Singapore.

Switzerland

The securities may not be publicly offered in Switzerland and will not be listed on the SIX Swiss Exchange ("SIX") or on any other stock exchange or regulated trading facility in Switzerland. This Offering Memorandum 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 Offering Memorandum nor any other offering or marketing material relating to the securities or the offering may be publicly distributed or otherwise made publicly available in Switzerland.

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

United Kingdom

This Offering Memorandum is only being distributed to, and is only directed at, persons in the United Kingdom that are qualified investors within the meaning of Article 2(1)(e) of the Prospectus Directive that are also (i) investment professionals falling within Article 19(5) of the Financial Services and Markets Act 2000 (Financial Promotion) Order 2005, as amended (the "Order") and/or (ii) high net worth entities falling within Article 49(2)(a) to (d) of the Order and other persons to whom it may lawfully be communicated (each such person being referred to as a "relevant person").

This Offering Memorandum and its contents are confidential and should not be distributed, published or reproduced (in whole or in part) or disclosed by recipients to any other persons in the United Kingdom. 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.

General Non-U.S. Legend

For offerings that are not marketed in any U.S. jurisdiction, include the following general non-U.S. legend as a lead-in to the other applicable legends below:

This Offering Memorandum is for use solely in connection with the proposed offering in certain jurisdictions. This Offering Memorandum is not to be distributed in any other jurisdiction and is not to be used in connection with any offer of, or any invitation or solicitation by or on behalf of the Company to subscribe for or purchase, securities in any other jurisdiction. This Offering Memorandum is personal to each offeree and does not constitute an offer to any person or to the public generally to subscribe for or otherwise acquire the securities. Distribution of this Offering Memorandum to any person other than the prospective investor and any person retained to advise such prospective investor with respect to its purchase is unauthorized.

Delivery of this Offering Memorandum shall not constitute an offer to sell or the solicitation of an offer to buy the securities described herein.

The distribution of this Offering Memorandum in certain jurisdictions may be restricted by law. You must inform yourself about, and observe, any such restrictions. You must comply with all applicable laws and regulations in force in any jurisdiction in which you purchase, offer or sell the securities or possess or distribute this Offering Memorandum and must obtain any consent, approval or permission required for your purchase, offer or sale of the securities under the laws and regulations in force in any jurisdiction to which you are subject or in which you make such purchases, offers or sales. We are not, and the Initial Purchaser is not, making an offer of, or invitation to purchase, any of the securities to any person in any jurisdiction in which such offer or solicitation would be unlawful.

This Offering Memorandum has not been submitted to the review or registration procedures of the SEC under the U.S. Securities Act of 1933 as amended (the "Act"), or otherwise, any regulatory authority in or outside the United States. The offering of the securities pursuant to this Offering Memorandum has not been approved or recommended by any governmental securities regulator.

LEGAL MATTERS

Cooley LLP, Boston, Massachusetts, will pass upon the validity of the issuance of the common stock offered hereby. The underwriter is being represented by Goodwin Procter LLP, Redwood City, California.

EXPERTS

The financial statements of ZIOPHARM Oncology, Inc. as of December 31, 2018 and 2017 and for each of the years in the three-year period ended December 31, 2018 and the effectiveness of internal control over financial reporting as of December 31, 2018, incorporated herein by reference from the ZIOPHARM Oncology, Inc. Annual Report on Form 10-K for the year ended December 31, 2018, have been audited by RSM US LLP, an independent registered public accounting firm, as stated in their report thereon (which report expresses an unqualified opinion) incorporated herein by reference, and have been incorporated herein in reliance upon such report and upon the authority of such firm as experts in accounting and auditing.

WHERE YOU CAN FIND MORE INFORMATION

We are a reporting company and file annual, quarterly and current reports, proxy statements and other information with the SEC. You may read and copy these reports, proxy statements and other information at the SEC's public reference room at 100 F Street, N.E., Washington, D.C. 20549 or at the SEC's other public reference facilities. Please call the SEC at 1-800-SEC-0330 for more information about the operation of the public reference rooms. You can request copies of these documents by writing to the SEC and paying a fee for the copying costs. In addition, the SEC maintains an Internet site at *http://www.sec.gov* that contains reports, proxy and information statements and other information regarding issuers that file electronically with the SEC. Our SEC filings are available on the SEC's Internet site. We maintain a website at *http://www.ziopharm.com*. Information found on, or accessible through, our website is not a part of, and is not incorporated into, this prospectus supplement or the accompanying prospectus, and you should not consider it part of this prospectus supplement or part of the accompanying prospectus.

INCORPORATION OF INFORMATION BY REFERENCE

We are allowed to incorporate by reference information contained in documents that we file with the SEC. This means that we can disclose important information to you by referring you to those documents and that the information in this prospectus supplement is not complete and you should read the information incorporated by reference for more detail. Information in this prospectus supplement supersedes information incorporated by reference that we filed with the SEC prior to the date of this prospectus supplement, while information that we file later with the SEC will automatically update and supersede the information in this prospectus supplement.

We incorporate by reference the documents listed below and any future filings we will make with the SEC under Section 13(a), 13(c), 14 or 15(d) of the Exchange Act from the date of this prospectus supplement but prior to the termination of the offering of the securities covered hereby (other than Current Reports or portions thereof furnished under Item 2.02 or 7.01 of Form 8-K):

- our Annual Report on Form 10-K for the fiscal year ended December 31, 2018, filed on April 5, 2019;
- The information specifically incorporated by reference into our Annual Report on Form 10-K for the fiscal year ended December 31, 2018 from our Definitive Proxy Statement on Schedule 14A, filed on April 29, 2019;
- our Quarterly Reports on Form 10-Q for the quarters ended March 31, 2019, June 30, 2019 and September 30, 2019, filed on May 5, 2019, August 8, 2019 and November 11, 2019, respectively;
- our Current Reports on Form 8-K filed on January 10, 2019 (other than the information furnished under Item 7.01 and exhibits related thereto), February 4, 2019, April 29, 2019, May 28, 2019, June 17, 2019, July 24, 2019, August 1, 2019, September 13, 2019 (other than the information furnished under Item 7.01 and exhibits related thereto) September 26, 2019 (other than the information furnished under Item 7.01 and exhibits related thereto), October 1, 2019, October 15, 2019, October 28, 2019 (other than the information furnished under Item 7.01 and exhibits related thereto), November 25, 2019 (other than the information furnished under Item 7.01 and exhibits related thereto); and
- The description of our common stock set forth in the registration statement on Form 8-A registering our common stock under Section 12 of the Exchange Act, which was filed with the SEC on September 20, 2006, including any amendments or reports filed for purposes of updating such description.

We will provide to each person, including any beneficial owner, to whom a prospectus is delivered a copy of any or all of the documents that are incorporated by reference in this prospectus supplement but not delivered with this prospectus, including exhibits that are specifically incorporated by reference in such documents. You may request a copy of such documents at no cost, by writing or telephoning us at the following address or telephone number:

ZIOPHARM Oncology, Inc.
One First Avenue, Parris Building 34, Navy Yard Plaza
Boston, Massachusetts 02129
Attention: Chief Legal Officer
Telephone: (617) 259-197

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PROSPECTUS

Common Stock
Preferred Stock
Debt Securities
Warrants

From time to time, we may offer and sell any combination of the securities described in this prospectus, either individually or in combination, at prices and on terms described in one or more supplements to this prospectus. We may also offer securities as may be issuable upon conversion, redemption, repurchase, exchange or exercise of any securities registered hereunder, including any applicable anti-dilution provisions.

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 offerings and securities in one or more supplements to this prospectus. We may also authorize one or more free writing prospectuses to be provided to you in connection with these offerings. The prospectus supplement and any related free writing prospectus may also add, update or change information contained in this prospectus. You should carefully read this prospectus, the applicable prospectus supplement and any related free writing prospectus, as well as any documents incorporated by reference, before buying any of the securities being offered.

This prospectus may not be used to consummate a sale of any securities unless accompanied by a prospectus supplement.

Our common stock is listed on the Nasdaq Capital Market under the symbol "ZIOP." On June 20, 2019, the closing price of our common stock, as reported on the Nasdaq Capital Market, was $5.82. The applicable prospectus supplement will contain information, where applicable, as to other listings, if any, on the Nasdaq Capital Market or other securities exchange of the securities covered by the prospectus supplement.

Securities may be sold to or through underwriters or dealers, directly to purchasers or through agents designated from time to time. For additional information on the methods of sale, you should refer to the section titled "Plan of Distribution" in this prospectus and in the applicable prospectus supplement. If any underwriters are involved in the sale of any securities with respect to which this prospectus is being delivered, the names of such underwriters and any applicable discounts or commissions and options to purchase additional shares will be set forth in a prospectus supplement. The price to the public of such securities and the net proceeds we expect to receive from such sale will also be set forth in a prospectus supplement.

Investing in our securities involves a high degree of risk. You should review carefully the risks and uncertainties described under the heading "Risk Factors" on page 9 of this prospectus and any similar section contained in the applicable prospectus supplement and in any free writing prospectuses we have authorized for use in connection with a specific offering, and under similar headings in the other documents that are incorporated by reference into this prospectus.

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

The date of this prospectus is June 21 , 2019.

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ABOUT THIS PROSPECTUS

This prospectus is part of an automatic registration statement on Form S-3 that we filed with the Securities and Exchange Commission, or SEC, using a "shelf" registration process as a "well-known seasoned issuer" as defined in Rule 405 under the Securities Act of 1933, as amended, or the Securities Act. Under this shelf registration statement, we may sell common stock, preferred stock, various series of debt securities, or warrants to purchase any of such securities, either individually or in combination with other securities described in this prospectus, in one or more offerings from time to time. Selling stockholders may offer and sell, in one or more offerings, shares of common stock as described in this prospectus or the applicable prospectus supplement. There is no limit on the aggregate amount of the securities that we or selling stockholders may offer pursuant to the registration statement of which this prospectus is a part. This prospectus provides you with a general description of the securities we, and the common stock selling stockholders, may offer.

Each time we sell any type or series of securities, or selling stockholders offer common stock, under this prospectus, we will provide a prospectus supplement that will include more specific information about the terms of that offering. We may also authorize one or more free writing prospectuses to be provided to you that may contain material information relating to these offerings. The prospectus supplement and any related free writing prospectus that we may authorize to be provided to you may also add, update or change any of the information contained in this prospectus or in the documents we have incorporated by reference into this prospectus. This prospectus, together with the applicable prospectus supplement, any related free writing prospectus and the documents incorporated by reference into this prospectus and the applicable prospectus supplement, will include all material information relating to the applicable offering. Before buying any of the securities being offered, we urge you to carefully read this prospectus, the applicable prospectus supplement and any related free writing prospectuses we have authorized for use in connection with a specific offering, together with the additional information incorporated herein by reference as described under the heading "Incorporation of Certain Information by Reference."

This prospectus may not be used to consummate a sale of securities unless it is accompanied by a prospectus supplement.

You should rely only on the information contained in, or incorporated by reference into, this prospectus and the applicable prospectus supplement, along with the information contained in any free writing prospectuses we have authorized for use in connection with a specific offering. We have not authorized anyone to provide you with different or additional information. This prospectus is an offer to sell only the securities offered hereby, but only under circumstances and in jurisdictions where it is lawful to do so.

The information appearing in this prospectus, any applicable prospectus supplement and any related free writing prospectus is accurate only as of the date on the front of the document and any information we have incorporated by reference is accurate only as of the date of the document incorporated by reference, regardless of the time of delivery of this prospectus, the prospectus supplement or any related free writing prospectus, or the time of any sale of a security.

This prospectus includes summaries of certain provisions contained in some of the documents described herein, but reference is made to the actual documents for complete information. All of the summaries are qualified in their entirety by the actual documents. Copies of some of the documents referred to herein have been filed, will be filed or will be incorporated by reference as exhibits to the registration statement of which this prospectus is a part, and you may obtain copies of those documents as described under the heading "Where You Can Find More Information."

Unless the context otherwise indicates, references in this prospectus to "Ziopharm," our "Company," "we," "us," "our" and similar terms refer to Ziopharm Oncology, Inc.

PROSPECTUS SUMMARY

This summary highlights selected information contained elsewhere in this prospectus or incorporated by reference into this prospectus, and does not contain all of the information that you need to consider in making your investment decision. You should carefully read the entire prospectus, the applicable prospectus supplement and any related free writing prospectus, including the risks of investing in our securities discussed under the heading "Risk Factors" contained in the applicable prospectus supplement and any related free writing prospectus, and under similar headings in the other documents that are incorporated by reference into this prospectus. You should also carefully read the information incorporated by reference into this prospectus, including our financial statements, and the exhibits to the registration statement of which this prospectus is a part.

Ziopharm Oncology, Inc.

Company Overview

We are a clinical-stage biopharmaceutical company focused on discovering, acquiring, developing and commercializing next generation immunotherapy platforms that leverage cell- and gene-based therapies to treat patients with cancer. We are developing two immuno-oncology platform technologies that utilize the immune system by employing novel, controlled gene expression and innovative cell engineering technologies designed to deliver safe, effective, and scalable non-viral cell- and viral-based gene therapies for the treatment of multiple cancer types. Our first platform is referred to as *Sleeping Beauty* and is based on the genetic engineering of immune cells using a non-viral transposon/transposase system that is intended to stably reprogram T cells outside of the body for subsequent infusion. Our second platform is termed Controlled IL-12, which is designed to stimulate expression of interleukin 12, or IL-12, a master regulator of the immune system, in a controlled and safe manner to focus the patient's immune system to attack cancer cells. We believe these two platforms have the potential to provide unique and powerful solutions to address the issues associated with (1) treating solid tumors with heterogeneous and unknown antigens, and (2) providing cost-effective scalable manufacturing solutions for T cell receptor T cell, or TCR$^+$ T, therapies for solid tumors and chimeric antigen receptor, or CAR T cell, or CAR$^+$ T, therapies targeting CD19 on malignant B cells. We expect programs from our two platform technologies to be in the clinic in 2019.

Using our *Sleeping Beauty* platform, we are developing TCR$^+$ T therapies initially to target solid tumors. Our T cell receptor, or TCR, program designs and manufactures T cells that are intended to target tumor-specific antigens, thereby delivering personalized therapy that can attack an individual patient's cancer. These antigens are referred to as neoantigens as they are only expressed by the tumor, reducing the potential for toxicity upon targeting normal cells. A minority of neoantigens are shared between patients and between classes of tumors and are referred to as "hotspots". The *Sleeping Beauty* system uses DNA plasmids to reprogram T cells to express introduced TCRs on a patient-by-patient basis (addressing inter-tumor heterogeneity) and possibly to express more than one TCR for each patient (addressing intra-tumor heterogeneity). The genetic modification of patient-derived T cells using the *Sleeping Beauty* system enables us to target neoantigens unique to a patient's tumor infusing recipient-derived (autologous) TCRs and shared neoantigens in hotspots using allogeneic TCRs derived from third parties. We believe the scalability of our approach provides a competitive advantage to alternative viral-based approaches to T cell manufacturing. Under our Cooperative Research and Development Agreement, or CRADA, the National Cancer Institute, or the NCI, intends to initiate a clinical trial in patients with a variety of solid tumors using the *Sleeping Beauty* platform to genetically modify T cells to target patient-specific neoantigens in mid-2019. The clinical trial will be under the direction of Steven A. Rosenberg, M.D., Ph.D., Chief of the Surgery Branch at the NCI.

We are also developing CAR$^+$ T therapies using our *Sleeping Beauty* platform. Our CAR$^+$ T program seeks to solve the complex and costly manufacturing limitations of existing CD19-specific CAR$^+$ T therapies that we

believe will continue limiting their commercial potential. We believe using DNA plasmids in the *Sleeping Beauty* system to express CAR and our proprietary membrane-bound interleukin 15, or mbIL15, in resting T cells obtained from peripheral blood will enable infused T cells to propagate within the patient to target leukemia and lymphoma, thus avoiding the need to numerically expand T cells for weeks in bioreactors before patient administration. The mbIL15 is co-expressed with a "kill switch" to conditionally eliminate infused T cells. We expect the lower cost of DNA plasmids compared with the virus used by other CAR+ T programs, together with the avoidance of lengthy *ex vivo* manufacturing, will reduce the cost and complexity of manufacturing CAR+ T cells. These technologies should enable T cells to be infused within two days of gene transfer in a process we refer to as rapid personalized manufacture, or RPM. We are advancing our CAR+ T therapies in the United States in collaboration with The University of Texas MD Anderson Cancer Center, or MD Anderson, to target CD19 on malignant B cells. In 2019, we hope to resolve our clinical hold with the U.S. Food and Drug Administration, or FDA, and initiate a Phase 1 clinical trial in the United States of our third-generation *Sleeping Beauty* modified CAR+ T cells, co-expressing CAR and mbIL15, manufactured and infused into the patient in less than two days from gene transfer. In addition, in a joint venture with TriArm Therapeutics, Ltd., or TriArm, we are forming Eden BioCell, Ltd., or Eden BioCell, to lead clinical development and commercialization of *Sleeping Beauty*-generated CD19-specific CAR-T therapies in the People's Republic of China, Taiwan and Korea. Eden BioCell will be owned equally by us and TriArm and the parties will share decision-making authority. TriArm has committed up to $35.0 million to this joint venture and will manage all clinical development to execute trials in the territory. We expect our joint venture with TriArm to close in mid-2019 and we may evaluate additional programs to pursue in this joint venture.

Our Controlled IL-12 platform uses virotherapy based on an engineered replication-incompetent adenovirus (Ad-RTS-hIL-12) plus veledimex as a gene delivery system to conditionally produce IL-12, a potent, naturally occurring anti-cancer protein, to treat patients with solid tumors where a specific target is unknown, including brain cancer. Our Controlled IL-12 platform allows us to deliver IL-12 in a tunable dose, which is critical for this potent cytokine. In a Phase 1 clinical trial of patients with recurrent glioblastoma multiforme, or rGBM, a subset of patients (n=6) who received low-dose steroids along with 20 mg of veledimex plus Ad-RTS-hIL-12, achieved 17.8 months median overall survival, or OS, compared with five to eight months OS established in historical controls. Thirty-six additional patients with rGBM have been recruited into a sub study designed to encourage use of low-dose steroids and 20 mg veledimex to further understand the potential of Controlled IL-12 as a monotherapy. We are also developing our Controlled IL-12 platform in combination with immune checkpoint inhibitors. In June 2018, we began enrolling patients with rGBM to receive Ad-RTS-hIL-12 plus veledimex in combination with OPDIVO® (nivolumab) in a phase 1 dose-escalation trial. In November 2018, we announced a clinical supply agreement with Regeneron Pharmaceuticals, Inc., or Regeneron, to evaluate Ad-RTS-hIL-12 plus veledimex in combination with Regeneron's PD-1antibody Libtayo® (cemiplimab-rwlc) for the treatment of patients with rGBM. We currently expect to initiate a phase 2 clinical trial in the first half of 2019 in approximately 30 patients with rGBM to measure preliminary safety and efficacy of Ad-RTS-hIL-12 plus veledimex in combination with Libtayo.

As of March 31, 2019, we had cash and cash equivalents of approximately $51.5 million. We expect that our existing cash and cash equivalents will be sufficient to fund our current operations into the second quarter of 2020, and we have no committed sources of additional capital at this time. The forecast of cash resources is forward-looking information that involves risks and uncertainties, and the actual amount of our expenses could vary materially and adversely as a result of a number of factors.

We have not generated significant revenue and have incurred significant net losses in each year since our inception. For the three months ended March 31, 2019, we had a net loss of $13.4 million, and, as of March 31, 2019, we have incurred approximately $579.8 million of accumulated deficit since our inception in 2003. We

expect to continue to incur significant operating expenditures and net losses. Further development of our product candidates will likely require substantial increases in our expenses as we:

- continue to undertake clinical trials for product candidates;
- seek regulatory approvals for product candidates;
- work with regulatory authorities to identify and address program-related inquiries;
- implement additional internal systems and infrastructure;
- hire additional personnel; and
- scale-up the formulation and manufacturing of our product candidates.

We continue to seek additional financial resources to fund the further development of our product candidates. If we are unable to obtain sufficient additional capital, one or more of these programs could be delayed, and we may be unable to continue our operations at planned levels and be forced to reduce our operations. Because of the numerous risks and uncertainties associated with product development, we are unable to predict the timing or amount of increased expenses or when or if we will be able to achieve or maintain profitability.

Recent Developments

Changes to Board of Directors

On June 13, 2019, Heidi Hagen was appointed to our board of directors. Also on June 13, 2019, Scott Braunstein, M.D., Laurence Cooper, M.D., Ph.D., Elan Ezickson, Douglas Pagán, and Scott Tarriff were elected to our board at our 2019 annual meeting of stockholders. James Cannon stepped down from our board when his term expired at our 2019 annual meeting of stockholders.

Clinical and Regulatory Developments

- On April 1, 2019, we announced that the FDA has granted Fast Track Designation for our Controlled IL-12 program which consists of Ad-RTS-hIL-12 plus veledimex, for the treatment of recurrent or progressive glioblastoma multiforme in adults. The FDA's Fast Track program is designed to facilitate the development and expedite the review of drugs that treat serious conditions and fill an unmet medical need.
- Enrollment continues in our Phase 1 clinical trial to evaluate Ad-RTS-hIL-12 plus veledimex in combination with OPDIVO® (nivolumab). The Data and Safety Monitoring Board for the clinical trial has authorized escalation to the third dosing cohort for this clinical trial.
- Under our CRADA, the NCI is undertaking a clinical trial with enrollment expected to begin in mid-2019. NCI is developing autologous peripheral blood lymphocytes genetically modified with the *Sleeping Beauty* system to express TCRs that recognize neoantigens expressed by patients' solid tumors. On June 11, 2019, we announced that the FDA had cleared the investigational new drug application submitted by the NCI for this clinical trial.
- Patients are being followed in a Phase 1 investigator-led trial at MD Anderson to infuse CD19-specific CAR^{+}T cells based on genetic modification with the *Sleeping Beauty* system for patients with B-cell leukemias and lymphomas. This second-generation trial explores T cell dosing and time to manufacture.
- On June 2, 2019, we announced the presentation of new interim analyses of clinical data from Ad-RTS-hIL-12 plus veledimex, both as monotherapy and in combination with a PD-1 inhibitor, for

the treatment of recurrent or progressive glioblastoma multiforme in adults, at the American Society for Clinical Oncology (ASCO) Annual Meeting.

Patent License Agreement with the NCI

On May 28, 2019, we entered into a patent license agreement, or the License, with the NCI. Pursuant to the License, we hold an exclusive, worldwide license to certain intellectual property to develop and commercialize patient-derived (autologous), peripheral blood T cell therapy products engineered by transposon-mediated gene transfer to express TCRs reactive to mutated KRAS, p53 and EGFR. In addition, pursuant to the License, we hold an exclusive, worldwide license to certain intellectual property for manufacturing technologies to develop and commercialize autologous, peripheral blood T cell therapy products engineered by non-viral gene transfer to express TCRs, as well as a non-exclusive, worldwide license to certain additional manufacturing technologies.

Pursuant to the terms of the License, we are required to pay the NCI a cash payment in the aggregate amount of $1,500,000, with a $500,000 payment due within sixty days of the execution date of the License and additional $500,000 payments due on the six- and twelve-month anniversaries of the License. We also agreed to reimburse the NCI for past patent expenses in the aggregate amount of approximately $46,000.

The terms of the License also require us to pay the NCI minimum annual royalties in the amount of $250,000, which amount will be reduced to $100,000 once the aggregate minimum annual royalties paid by us equals $1,500,000. The first minimum annual royalty payment is payable on the date that is eighteen months following the date of the License.

We are also required to make performance-based payments upon successful completion of clinical and regulatory benchmarks relating to the licensed products. The aggregate potential benchmark payments are $4.3 million, of which aggregate payments of $3.0 million are due only after marketing approval in the United States or in Europe, Japan, Australia, China or India. The first benchmark payment of $100,000 will be due upon the initiation of our first sponsored Phase 1 clinical trial of a licensed product or licensed process in the field of use licensed under the License.

In addition, we are required to pay the NCI one-time benchmark payments following aggregate net sales of licensed products at certain net sales up to $1.0 billion. The aggregate potential amount of these benchmark payments is $12.0 million. We must also pay the NCI royalties on net sales of products covered by the License at rates in the low to mid-single digits depending upon the technology included in a licensed product. To the extent we enter into a sublicensing agreement relating to a licensed product, we are required to pay the NCI a percentage of all consideration received from a sublicensee, which percentage will decrease based on the stage of development of the licensed product at the time of the sublicense.

The License will expire upon expiration of the last patent contained in the licensed patent rights, unless terminated earlier. The NCI may terminate or modify the License in the event of a material breach, including if we do not meet certain milestones by certain dates, or upon certain insolvency events that remain uncured following the date that is 90 days following written notice of such breach or insolvency event. We may terminate the License, or any portion thereof, in our sole discretion at any time upon 60 days' written notice to the NCI. In addition, the NCI has the right to require us to sublicense the rights to the product candidates covered by the License upon certain conditions, including if we are not reasonably satisfying required health and safety needs or if we are not satisfying requirements for public use as specified by federal regulations.

Corporate Information

We originally incorporated in Colorado in September 1998 (under the name Net Escapes, Inc.) and later changed our name to "EasyWeb, Inc." in February 1999. We re-incorporated in Delaware on May 16, 2005 under

the same name. On September 13, 2005, we completed a "reverse" acquisition of privately held ZIOPHARM, Inc., a Delaware corporation. To effect this transaction, we caused ZIO Acquisition Corp., our wholly-owned subsidiary, to merge with and into ZIOPHARM, Inc., with ZIOPHARM, Inc. surviving as our wholly owned subsidiary. In accordance with the terms of the merger, the outstanding common stock of ZIOPHARM, Inc. automatically converted into the right to receive an aggregate of approximately 97.3% of our outstanding common stock (after giving effect to the transaction). Following the merger, we caused ZIOPHARM, Inc. to merge with and into us and we changed our name to "ZIOPHARM Oncology, Inc." Although EasyWeb, Inc. was the legal acquirer in the transaction, we accounted for the transaction as a reverse acquisition under generally accepted accounting principles. As a result, ZIOPHARM, Inc. became the registrant with the Commission and the historical financial statements of ZIOPHARM, Inc. became our historical financial statements.

Our principal executive offices are located at One First Avenue, Parris Building 34, Navy Yard Plaza, Boston, Massachusetts 02129, and our telephone number is (617) 259-1970. Our internet site is www.ziopharm.com. Information found on, or accessible through, our website is not a part of, and is not incorporated into, this prospectus, and you should not consider it part of this prospectus or part of any prospectus supplement.

The Securities We May Offer

We may offer shares of our common stock and preferred stock, various series of debt securities and warrants to purchase any of such securities, from time to time in one or more offerings under this prospectus, together with any applicable prospectus supplement and any related free writing prospectus, at prices and on terms to be determined by market conditions at the time of the relevant offering. This prospectus provides you with a general description of the securities we may offer. Each time we offer a type or series of securities under this prospectus, we will provide a prospectus supplement that will describe the specific amounts, prices and other important terms of the securities, including, to the extent applicable:

- designation or classification;
- aggregate principal amount or aggregate offering price;
- maturity;
- original issue discount, if any;
- rates and times of payment of interest or dividends, if any;
- redemption, conversion, exchange or sinking fund terms, if any;
- conversion or exchange prices or rates, if any, and, if applicable, any provisions for changes to or adjustments in the conversion or exchange prices or rates and in the securities or other property receivable upon conversion or exchange;
- ranking;
- restrictive covenants, if any;
- voting or other rights, if any; and
- important U.S. federal income tax considerations.

The prospectus supplement and any related free writing prospectus that we may authorize to be provided to you may also add, update or change information contained in this prospectus or in documents we have incorporated by reference. However, no prospectus supplement or free writing prospectus will offer a security that is not registered and described in this prospectus at the time of the effectiveness of the registration statement of which this prospectus is a part.

This prospectus may not be used to consummate a sale of securities unless it is accompanied by a prospectus supplement.

We may sell the securities directly to investors or through underwriters, dealers or agents. We, and our underwriters or agents, reserve the right to accept or reject all or part of any proposed purchase of securities. If we do offer securities through underwriters or agents, we will include in the applicable prospectus supplement:

- the names of those underwriters or agents;
- applicable fees, discounts and commissions to be paid to them;
- details regarding over-allotment options, if any; and
- the estimated net proceeds to us.

Common Stock. We may issue shares of our common stock from time to time. Each holder of common stock is entitled to one vote for each share on all matters submitted to a vote of the stockholders and does not have cumulative voting rights. Subject to preferences that may apply to any outstanding preferred stock, holders of our common stock are entitled to receive ratably any dividends that our board of directors may declare out of funds legally available for that purpose. In the event of our liquidation, dissolution or winding up, holders of our common stock are entitled to share ratably in all assets remaining after payment of liabilities and the liquidation preference of any outstanding preferred stock. Holders of our common stock have no preemptive, conversion, subscription or other rights, and there are no redemption or sinking fund provisions applicable to our common stock. The rights, preferences and privileges of the holders of our common stock are subject to and may be adversely affected by the rights of the holders of shares of any series of our preferred stock that we may designate in the future. In this prospectus, we have summarized certain general features of our common stock under the heading “Description of Capital Stock—Common Stock.” We urge you, however, to read the applicable prospectus supplement (and any related free writing prospectus that we may authorize to be provided to you) related to any common stock being offered.

Preferred Stock. We may issue shares of our preferred stock from time to time, in one or more series. Under our certificate of incorporation, our board of directors has the authority, without further action by the stockholders (unless such stockholder action is required by applicable law or the rules of any stock exchange or market on which our securities are then traded), to designate up to 30,000,000 shares of preferred stock in one or more series and to determine the designations, voting powers, preferences and rights of each series of the preferred stock, as well as the qualifications, limitations or restrictions thereof, including dividend rights, conversion rights, preemptive rights, terms of redemption or repurchase, liquidation preferences, sinking fund terms and the number of shares constituting any series or the designation of any series, any or all of which may be greater than the rights of the common stock. Any convertible preferred stock we may issue will be convertible into our common stock or exchangeable for our other securities. Conversion may be mandatory or at the holder’s option and would be at prescribed conversion rates.

If we sell any series of preferred stock under this prospectus, we will fix the designations, voting powers, preferences and rights of such series of preferred stock, as well as the qualifications, limitations or restrictions thereof, in the certificate of designation relating to that series. We will file as an exhibit to the registration statement of which this prospectus is a part, or will incorporate by reference from reports that we file with the SEC, the form of any certificate of designation that describes the terms of the series of preferred stock that we are offering before the issuance of the related series of preferred stock. In this prospectus, we have summarized certain general features of the preferred stock under the heading “Description of Capital Stock —Preferred Stock.” We urge you, however, to read the applicable prospectus supplement (and any free writing prospectus that we may authorize to be provided to you) related to the series of preferred stock being offered, as well as the complete certificate of designation that contains the terms of the applicable series of preferred stock.

Debt Securities. We may issue debt securities from time to time, in one or more series, as either senior or subordinated debt or as senior or subordinated convertible debt. The senior debt securities will rank equally with any other unsecured and unsubordinated debt. The subordinated debt securities will be subordinate and junior in right of payment, to the extent and in the manner described in the instrument governing the debt, to all of our senior indebtedness. Convertible debt securities will be convertible into or exchangeable for our common stock or preferred stock. Conversion may be mandatory or at the holder's option and would be at prescribed conversion rates.

The debt securities will be issued under one or more documents called indentures, which are contracts between us and a national banking association or other eligible party, as trustee. In this prospectus, we have summarized certain general features of the debt securities under the heading "Description of Debt Securities." We urge you, however, to read the applicable prospectus supplement (and any free writing prospectus that we may authorize to be provided to you) related to the series of debt securities being offered, as well as the complete indentures that contain the terms of the debt securities. We have filed a form of indenture as an exhibit to the registration statement of which this prospectus is a part. We will file as exhibits to the registration statement of which this prospectus is a part, or will be incorporated by reference from reports that we file with the SEC, supplemental indentures and forms of debt securities containing the terms of the debt securities being offered.

Warrants. We may issue warrants for the purchase of common stock, preferred stock or debt securities, in one or more series, from time to time. We may issue warrants independently or in combination with common stock, preferred stock or debt securities. In this prospectus, we have summarized certain general features of the warrants under the heading "Description of Warrants." We urge you, however, to read the applicable prospectus supplement (and any free writing prospectus that we may authorize to be provided to you) related to the particular series of warrants being offered, as well as the complete warrant agreements and warrant certificates that contain the terms of the warrants. We have filed forms of the warrant agreements and forms of warrant certificates containing the terms of the warrants that we may offer as exhibits to the registration statement of which this prospectus is a part. We will file as exhibits to the registration statement of which this prospectus is a part, or will be incorporated by reference from reports that we file with the SEC, the form of warrant or the warrant agreement and warrant certificate, as applicable, that contain the terms of the particular series of warrants we are offering, and any supplemental agreements, before the issuance of such warrants.

Any warrants issued under this prospectus may be evidenced by warrant certificates. Warrants may be issued under a warrant agreement that we enter into with a warrant agent. We will indicate the name and address of the warrant agent, if applicable, in the prospectus supplement relating to the particular series of warrants being offered.

RISK FACTORS

Investing in our securities involves a high degree of risk. You should carefully review the risks and uncertainties described under the heading "Risk Factors" contained in the applicable prospectus supplement and any related free writing prospectus, and under similar headings in our Annual Report on Form 10-K for the year ended December 31, 2018 and in our most recent Quarterly Report on Form 10-Q, as updated by our subsequent filings, which are incorporated by reference into this prospectus, before deciding whether to purchase any of the securities being registered pursuant to the registration statement of which this prospectus is a part. Each of the risk factors could adversely affect our business, results of operations, financial condition and cash flows, as well as adversely affect the value of an investment in our securities, and the occurrence of any of these risks might cause you to lose all or part of your investment. Additional risks not presently known to us or that we currently believe are immaterial may also significantly impair our business operations.

SPECIAL NOTE REGARDING FORWARD-LOOKING STATEMENTS

This prospectus and the documents incorporated by reference contain forward-looking statements. These are based on our management's current beliefs, expectations and assumptions about future events, conditions and results and on information currently available to us. Discussions containing these forward-looking statements may be found, among other places, in the sections titled "Business," "Risk Factors" and "Management's Discussion and Analysis of Financial Condition and Results of Operations" incorporated by reference from our most recent Annual Report on Form 10-K, as well as any amendments thereto, filed with the SEC.

Any statements in this prospectus, or incorporated herein, about our expectations, beliefs, plans, objectives, assumptions or future events or performance are not historical facts and are forward-looking statements. Within the meaning of Section 27A of the Securities Act and Section 21E of the Securities Exchange Act of 1934, as amended, or the Exchange Act, these forward-looking statements include statements regarding:

- our ability to raise substantial additional capital to fund our planned operations and to continue as a going concern;
- our estimates regarding expenses, use of cash, timing of future cash needs and capital requirements;
- the development of our product candidates, including statements regarding the timing of initiation, completion and the outcome of clinical studies or trials and related preparatory work and the period during which the results of the trials will become available;
- our ability to advance our product candidates through various stages of development, especially through pivotal safety and efficacy trials;
- the risk that final trial data may not support interim analysis of the viability of our product candidates;
- our expectation regarding the safety and efficacy of our product candidates;
- the progress and timing of our research and development programs;
- the timing, scope or likelihood of regulatory filings and approvals from the U.S. Food and Drug Administration or equivalent foreign regulatory agencies for our product candidates and for which indications;
- our ability to license additional intellectual property relating to our product candidates from third parties and to comply with our existing license agreement;
- our ability to achieve the results contemplated by our collaboration agreements and the benefits to be derived from relationships with collaborators;
- developments and projections relating to competition from other pharmaceutical and biotechnology companies or our industry;

- our estimates regarding the potential market opportunity for our product candidates;
- the anticipated rate and degree of market acceptance of our product candidates for any indication if approved;
- the anticipated amount, timing and accounting of deferred revenues, milestones and other payments under licensing, collaboration or acquisition agreements, research and development costs and other expenses;
- our intellectual property position, including the strength and enforceability of our intellectual property rights;
- our ability to attract and retain qualified employees and key personnel; and
- the impact of government laws and regulations in the United States and foreign countries.

In some cases, you can identify forward-looking statements by terms such as “may”, “will”, “should”, “could”, “would”, “expects”, “plans”, “anticipates”, “believes”, “estimates”, “projects”, “predicts”, “potential” and similar expressions intended to identify forward-looking statements. These statements reflect our current views with respect to future events and are based on assumptions and subject to risks and uncertainties. Given these uncertainties, you should not place undue reliance on these forward-looking statements. We discuss many of these risks in greater detail under the heading “Risk Factors” in the applicable prospectus supplement or free writing prospectus and in our reports filed from time to time under the Securities Act and/or the Exchange Act. We encourage you to read these filings as they are made. Also, these forward-looking statements represent our estimates and assumptions only as of the date of the document containing the applicable statement.

You should refer to the “Risk Factors” section contained in the applicable prospectus supplement and any related free writing prospectus, and under similar headings in the other documents that are incorporated by reference into this prospectus, for a discussion of important factors that may cause our actual results to differ materially from those expressed or implied by our forward-looking statements. Given these risks, uncertainties and other factors, many of which are beyond our control, we cannot assure you that the forward-looking statements in this prospectus will prove to be accurate, and you should not place undue reliance on these forward-looking statements. Furthermore, if our forward-looking statements prove to be inaccurate, the inaccuracy may be material. In light of the significant uncertainties in these forward-looking statements, you should not regard these statements as a representation or warranty by us or any other person that we will achieve our objectives and plans in any specified time frame, or at all.

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

USE OF PROCEEDS

We will retain broad discretion over the use of the net proceeds from the sale of our securities offered by this prospectus. Unless we indicate otherwise in the applicable prospectus supplement or in any related free writing prospectus we have authorized for use in connection with a specific offering, we anticipate that any net proceeds will be used for working capital and general corporate purposes. We may also use a portion of the net proceeds to invest in or acquire businesses or technologies that we believe are complementary to our own. We will set forth in the applicable prospectus supplement or free writing prospectus our intended use for the net proceeds received from the sale of any securities sold pursuant to the prospectus supplement or free writing prospectus. Pending these uses, we intend to invest the net proceeds in investment-grade, interest-bearing securities.

DILUTION

We will set forth in a prospectus supplement the following information regarding any material dilution of the equity interests of investors purchasing securities in an offering under this prospectus:

- the net tangible book value per share of our equity securities before and after the offering;
- the amount of the increase in such net tangible book value per share attributable to the cash payments made by purchasers in the offering; and
- the amount of the immediate dilution from the public offering price which will be absorbed by such purchasers.

DESCRIPTION OF CAPITAL STOCK

The following description of our capital stock and provisions of our amended and restated certificate of incorporation and amended and restated bylaws are summaries. You should also refer to the amended and restated certificate of incorporation and the amended and restated bylaws, which are filed as exhibits to the registration statement of which this prospectus is part.

General

As of the date of this prospectus, our authorized capital stock consists of 280,000,000 shares, comprised of 250,000,000 shares of common stock, par value $0.001 per share, and 30,000,000 shares of preferred stock, par value $0.001 per share. As of June 18, 2019, there were 161,319,096 shares of common stock and no shares of preferred stock issued and outstanding. Our common stock is traded on the Nasdaq Capital Market under the symbol “ZIOP”.

Common Stock

Voting Rights. The holders of our common stock are entitled to one vote for each outstanding share of common stock owned by such stockholder on every matter properly submitted to the stockholders for their vote. Stockholders are not entitled to vote cumulatively for the election of directors. Because of this, the holders of a majority of the shares of common stock entitled to vote in any election of directors can elect all of the directors standing for election, if they should so choose. At any meeting of the stockholders, a quorum as to any matter shall consist of a majority of the votes entitled to be cast on the matter, except where a larger quorum is required by law, by our certificate of incorporation or by our bylaws.

Dividend Rights. Holders of our common stock are entitled to receive ratably dividends and other distributions of cash or any other right or property as may be declared by our board of directors out of our assets or funds legally available for such dividends or distributions. The dividend rights of holders of common stock are subject to the dividend rights of the holders of any series of preferred stock that may be issued and outstanding from time to time.

Liquidation Rights. In the event of any voluntary or involuntary liquidation, dissolution or winding up of our affairs, holders of our common stock would be entitled to share ratably in our assets that are legally available for distribution to stockholders after payment of liabilities. If we have any preferred stock outstanding at such time, the holders of such preferred stock may be entitled to distribution and/or liquidation preferences that require us to pay the applicable distribution to the holders of preferred stock before paying distributions to the holders of common stock.

Rights and Preferences. Holders of our common stock have no preemptive, conversion or subscription rights, and there are no redemption or sinking fund provisions applicable to our common stock. The rights, preferences and privileges of the holders of common stock are subject to, and may be adversely affected by, the rights of the holders of shares of any series of our preferred stock that we may designate and issue in the future.

The transfer agent and registrar for our common stock is American Stock Transfer & Trust Company.

See “Certain Provisions of Delaware Law, the Certificate of Incorporation and Bylaws” for a description of provisions of our certificate of incorporation and bylaws which may have the effect of delaying, deferring or preventing changes in the our control.

Preferred Stock

Pursuant to our amended and restated certificate of incorporation, our board of directors has the authority, without stockholder approval, subject to limitations prescribed by law, to provide for the issuance of up to

30,000,000 shares of preferred stock in one or more series, and by filing a certificate pursuant to the applicable law of the State of Delaware, to establish from time to time the number of shares to be included in each such series, and to fix the designation, powers, preferences and rights of the shares of each series and any qualifications, limitations or restrictions thereof, and to increase or decrease the number of shares of any such series, but not below the number of shares of such series then outstanding.

We will fix the designations, voting powers, preferences and rights of the preferred stock of each series, as well as the qualifications, limitations or restrictions thereof, in the certificate of designation relating to that series. We will file as an exhibit to the registration statement of which this prospectus is a part, or will incorporate by reference from reports that we file with the Commission, the form of any certificate of designation that describes the terms of the series of preferred stock we are offering before the issuance of that series of preferred stock. This description will include:

- the title and stated value;
- the number of shares offered;
- the liquidation preference per share;
- the purchase price per share;
- the dividend rate(s), period(s) and/or payment date(s) or method(s) of calculation for dividends;
- whether dividends are cumulative or non-cumulative and, if cumulative, the date from which dividends will accumulate;
- our right, if any, to defer payment of dividends and the maximum length of any such deferral period;
- the procedures for any auction and remarketing, if any;
- the provisions for a sinking fund, if any;
- the provision for redemption or repurchase, if applicable, and any restrictions on our ability to exercise those redemption and repurchase rights;
- any listing of the preferred stock on any securities exchange or market;
- the terms and conditions, if applicable, upon which the preferred stock will be convertible into common stock, including the conversion price (or manner of calculation) and conversion period;
- whether the preferred stock will be exchangeable into debt securities, and, if applicable, the exchange price, or how it will be calculated, and the exchange period;
- voting rights, if any, of the preferred stock;
- preemptive rights, if any;
- restrictions on transfer, sale or other assignment, if any;
- whether interests in the preferred stock will be represented by depositary shares;
- a discussion of any material and/or special U.S. federal income tax considerations applicable to the preferred stock;
- the relative ranking and preferences of the preferred stock as to dividend rights and rights upon the liquidation, dissolution or winding up of our affairs;
- any limitations on issuance of any class or series of preferred stock ranking senior to or on a parity with the class or series of preferred stock as to dividend rights and rights upon liquidation, dissolution or winding up of our affairs; and
- any other specific terms, preferences, rights, limitations or restrictions of the preferred stock.

Our board of directors could authorize the issuance of shares of preferred stock with terms and conditions that could have the effect of discouraging a takeover or other transaction that might involve a premium price for holders of the shares or which holders might believe to be in their best interests. The issuance of preferred stock could adversely affect the voting power, conversion or other rights of holders of common stock and reduce the likelihood that common stockholders will receive dividend payments and payments upon liquidation.

The laws of the state of Delaware, the state of our incorporation, provide that the holders of preferred stock will have the right to vote separately as a class on any proposal involving fundamental changes in the rights of holders of such preferred stock. This right is in addition to any voting rights that may be provided for in the applicable certificate of designation.

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

DESCRIPTION OF DEBT SECURITIES

We may issue debt securities from time to time, in one or more series, as either senior or subordinated debt or as senior or subordinated convertible debt. While the terms we have summarized below will apply generally to any debt securities that we may offer under this prospectus, we will describe the particular terms of any debt securities that we may offer in more detail in the applicable prospectus supplement. The terms of any debt securities offered under a prospectus supplement may differ from the terms described below. Unless the context requires otherwise, whenever we refer to the indenture, we also are referring to any supplemental indentures that specify the terms of a particular series of debt securities.

We will issue the debt securities under the indenture that we will enter into with the trustee named in the indenture. The indenture will be qualified under the Trust Indenture Act of 1939, as amended, or the Trust Indenture Act. We have filed the form of indenture as an exhibit to the registration statement of which this prospectus is a part, and supplemental indentures and forms of debt securities containing the terms of the debt securities being offered will be filed as exhibits to the registration statement of which this prospectus is a part or will be incorporated by reference from reports that we file with the SEC.

The following summary of material provisions of the debt securities and the indenture is subject to, and qualified in its entirety by reference to, all of the provisions of the indenture applicable to a particular series of debt securities. We urge you to read the applicable prospectus supplements and any related free writing prospectuses related to the debt securities that we may offer under this prospectus, as well as the complete indenture that contains the terms of the debt securities.

General

The indenture does not limit the amount of debt securities that we may issue. It provides that we may issue debt securities up to the principal amount that we may authorize and may be in any currency or currency unit that we may designate. Except for the limitations on consolidation, merger and sale of all or substantially all of our assets contained in the indenture, the terms of the indenture do not contain any covenants or other provisions designed to give holders of any debt securities protection against changes in our operations, financial condition or transactions involving us.

We may issue the debt securities issued under the indenture as “discount securities,” which means they may be sold at a discount below their stated principal amount. These debt securities, as well as other debt securities that are not issued at a discount, may be issued with “original issue discount,” or OID, for U.S. federal income tax purposes because of interest payment and other characteristics or terms of the debt securities. Material U.S. federal income tax considerations applicable to debt securities issued with OID will be described in more detail in any applicable prospectus supplement.

We will describe in the applicable prospectus supplement the terms of the series of debt securities being offered, including:

- the title of the series of debt securities;
- any limit upon the aggregate principal amount that may be issued;
- the maturity date or dates;
- the form of the debt securities of the series;
- the applicability of any guarantees;
- whether or not the debt securities will be secured or unsecured, and the terms of any secured debt;
- whether the debt securities rank as senior debt, senior subordinated debt, subordinated debt or any combination thereof, and the terms of any subordination;

- if the price (expressed as a percentage of the aggregate principal amount thereof) at which such debt securities will be issued is a price other than the principal amount thereof, the portion of the principal amount thereof payable upon declaration of acceleration of the maturity thereof, or if applicable, the portion of the principal amount of such debt securities that is convertible into another security or the method by which any such portion shall be determined;
- the interest rate or rates, which may be fixed or variable, or the method for determining the rate and the date interest will begin to accrue, the dates interest will be payable and the regular record dates for interest payment dates or the method for determining such dates;
- our right, if any, to defer payment of interest and the maximum length of any such deferral period;
- if applicable, the date or dates after which, or the period or periods during which, and the price or prices at which, we may, at our option, redeem the series of debt securities pursuant to any optional or provisional redemption provisions and the terms of those redemption provisions;
- the date or dates, if any, on which, and the price or prices at which we are obligated, pursuant to any mandatory sinking fund or analogous fund provisions or otherwise, to redeem, or at the holder's option to purchase, the series of debt securities and the currency or currency unit in which the debt securities are payable;
- the denominations in which we will issue the series of debt securities, if other than denominations of $1,000 and any integral multiple thereof;
- any and all terms, if applicable, relating to any auction or remarketing of the debt securities of that series and any security for our obligations with respect to such debt securities and any other terms which may be advisable in connection with the marketing of debt securities of that series;
- whether the debt securities of the series shall be issued in whole or in part in the form of a global security or securities; the terms and conditions, if any, upon which such global security or securities may be exchanged in whole or in part for other individual securities; and the depositary for such global security or securities;
- if applicable, the provisions relating to conversion or exchange of any debt securities of the series and the terms and conditions upon which such debt securities will be so convertible or exchangeable, including the conversion or exchange price, as applicable, or how it will be calculated and may be adjusted, any mandatory or optional (at our option or the holders' option) conversion or exchange features, the applicable conversion or exchange period and the manner of settlement for any conversion or exchange;
- if other than the full principal amount thereof, the portion of the principal amount of debt securities of the series which shall be payable upon declaration of acceleration of the maturity thereof;
- additions to or changes in the covenants applicable to the particular debt securities being issued, including, among others, the consolidation, merger or sale covenant;
- additions to or changes in the events of default with respect to the securities and any change in the right of the trustee or the holders to declare the principal, premium, if any, and interest, if any, with respect to such securities to be due and payable;
- additions to or changes in or deletions of the provisions relating to covenant defeasance and legal defeasance;
- additions to or changes in the provisions relating to satisfaction and discharge of the indenture;
- additions to or changes in the provisions relating to the modification of the indenture both with and without the consent of holders of debt securities issued under the indenture;
- the currency of payment of debt securities if other than U.S. dollars and the manner of determining the equivalent amount in U.S. dollars;

- whether interest will be payable in cash or additional debt securities at our or the holders' option and the terms and conditions upon which the election may be made;
- the terms and conditions, if any, upon which we will pay amounts in addition to the stated interest, premium, if any and principal amounts of the debt securities of the series to any holder that is not a "United States person" for federal tax purposes;
- any restrictions on transfer, sale or assignment of the debt securities of the series; and
- any other specific terms, preferences, rights or limitations of, or restrictions on, the debt securities, any other additions or changes in the provisions of the indenture, and any terms that may be required by us or advisable under applicable laws or regulations.

Conversion or Exchange Rights

We will set forth in the applicable prospectus supplement the terms on which a series of debt securities may be convertible into or exchangeable for our common stock or our other securities. We will include provisions as to settlement upon conversion or exchange and whether conversion or exchange is mandatory, at the option of the holder or at our option. We may include provisions pursuant to which the number of shares of our common stock or our other securities that the holders of the series of debt securities receive would be subject to adjustment.

Consolidation, Merger or Sale

Unless we provide otherwise in the prospectus supplement applicable to a particular series of debt securities, the indenture will not contain any covenant that restricts our ability to merge or consolidate, or sell, convey, transfer or otherwise dispose of our assets as an entirety or substantially as an entirety. However, any successor to or acquirer of such assets (other than a subsidiary of ours) must assume all of our obligations under the indenture or the debt securities, as appropriate.

Events of Default under the Indenture

Unless we provide otherwise in the prospectus supplement applicable to a particular series of debt securities, the following are events of default under the indenture with respect to any series of debt securities that we may issue:

- if we fail to pay any installment of interest on any series of debt securities, as and when the same shall become due and payable, and such default continues for a period of 90 days; provided, however, that a valid extension of an interest payment period by us in accordance with the terms of any indenture supplemental thereto shall not constitute a default in the payment of interest for this purpose;
- if we fail to pay the principal of, or premium, if any, on any series of debt securities as and when the same shall become due and payable whether at maturity, upon redemption, by declaration or otherwise, or in any payment required by any sinking or analogous fund established with respect to such series; provided, however, that a valid extension of the maturity of such debt securities in accordance with the terms of any indenture supplemental thereto shall not constitute a default in the payment of principal or premium, if any;
- if we fail to observe or perform any other covenant or agreement contained in the debt securities or the indenture, other than a covenant specifically relating to another series of debt securities, and our failure continues for 90 days after we receive written notice of such failure, requiring the same to be remedied and stating that such is a notice of default thereunder, from the trustee or holders of at least 25% in aggregate principal amount of the outstanding debt securities of the applicable series; and
- if specified events of bankruptcy, insolvency or reorganization occur.

If an event of default with respect to debt securities of any series occurs and is continuing, other than an event of default specified in the last bullet point above, the trustee or the holders of at least 25% in aggregate principal amount of the outstanding debt securities of that series, by notice to us in writing, and to the trustee if notice is given by such holders, may declare the unpaid principal of, premium, if any, and accrued interest, if any, due and payable immediately. If an event of default specified in the last bullet point above occurs with respect to us, the principal amount of and accrued interest, if any, of each issue of debt securities then outstanding shall be due and payable without any notice or other action on the part of the trustee or any holder.

The holders of a majority in principal amount of the outstanding debt securities of an affected series may waive any default or event of default with respect to the series and its consequences, except defaults or events of default regarding payment of principal, premium, if any, or interest, unless we have cured the default or event of default in accordance with the indenture. Any waiver shall cure the default or event of default.

Subject to the terms of the indenture, if an event of default under an indenture shall occur and be continuing, the trustee will be under no obligation to exercise any of its rights or powers under such indenture at the request or direction of any of the holders of the applicable series of debt securities, unless such holders have offered the trustee reasonable indemnity. The holders of a majority in principal amount of the outstanding debt securities of any series will have the right to 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 the debt securities of that series, provided that:

- the direction so given by the holder is not in conflict with any law or the applicable indenture; and
- subject to its duties under the Trust Indenture Act, the trustee need not take any action that might involve it in personal liability or might be unduly prejudicial to the holders not involved in the proceeding.

A holder of the debt securities of any series will have the right to institute a proceeding under the indenture or to appoint a receiver or trustee, or to seek other remedies only if:

- the holder has given written notice to the trustee of a continuing event of default with respect to that series;
- the holders of at least 25% in aggregate principal amount of the outstanding debt securities of that series have made written request,
- such holders have offered to the trustee indemnity satisfactory to it against the costs, expenses and liabilities to be incurred by the trustee in compliance with the request; and
- the trustee does not institute the proceeding, and does not receive from the holders of a majority in aggregate principal amount of the outstanding debt securities of that series other conflicting directions within 90 days after the notice, request and offer.

These limitations do not apply to a suit instituted by a holder of debt securities if we default in the payment of the principal, premium, if any, or interest on, the debt securities.

We will periodically file statements with the trustee regarding our compliance with specified covenants in the indenture.

Modification of Indenture; Waiver

We and the trustee may change an indenture without the consent of any holders with respect to specific matters:

- to cure any ambiguity, defect or inconsistency in the indenture or in the debt securities of any series;

- to comply with the provisions described above under “Description of Debt Securities — Consolidation, Merger or Sale;”
- to provide for uncertificated debt securities in addition to or in place of certificated debt securities;
- to add to our covenants, restrictions, conditions or provisions such new covenants, restrictions, conditions or provisions for the benefit of the holders of all or any series of debt securities, to make the occurrence, or the occurrence and the continuance, of a default in any such additional covenants, restrictions, conditions or provisions an event of default or to surrender any right or power conferred upon us in the indenture;
- to add to, delete from or revise the conditions, limitations, and restrictions on the authorized amount, terms, or purposes of issue, authentication and delivery of debt securities, as set forth in the indenture;
- to make any change that does not adversely affect the interests of any holder of debt securities of any series in any material respect;
- to provide for the issuance of and establish the form and terms and conditions of the debt securities of any series as provided above under “Description of Debt Securities — General” to establish the form of any certifications required to be furnished pursuant to the terms of the indenture or any series of debt securities, or to add to the rights of the holders of any series of debt securities;
- to evidence and provide for the acceptance of appointment under any indenture by a successor trustee; or
- to comply with any requirements of the SEC in connection with the qualification of any indenture under the Trust Indenture Act.

In addition, under the indenture, the rights of holders of a series of debt securities may be changed by us and the trustee with the written consent of the holders of at least a majority in aggregate principal amount of the outstanding debt securities of each series that is affected. However, unless we provide otherwise in the prospectus supplement applicable to a particular series of debt securities, we and the trustee may make the following changes only with the consent of each holder of any outstanding debt securities affected:

- extending the fixed maturity of any debt securities of any series;
- reducing the principal amount, reducing the rate of or extending the time of payment of interest, or reducing any premium payable upon the redemption of any series of any debt securities; or
- reducing the percentage of debt securities, the holders of which are required to consent to any amendment, supplement, modification or waiver.

Discharge

Each indenture provides that we can elect to be discharged from our obligations with respect to one or more series of debt securities, except for specified obligations, including obligations to:

- provide for payment;
- register the transfer or exchange of debt securities of the series;
- replace stolen, lost or mutilated debt securities of the series;
- pay principal of and premium and interest on any debt securities of the series;
- maintain paying agencies;
- hold monies for payment in trust;
- recover excess money held by the trustee;

- compensate and indemnify the trustee; and
- appoint any successor trustee.

In order to exercise our rights to be discharged, we must deposit with the trustee money or government obligations sufficient to pay all the principal of, any premium, if any, and interest on, the debt securities of the series on the dates payments are due.

Form, Exchange and Transfer

We will issue the debt securities of each series only in fully registered form without coupons and, unless we provide otherwise in the applicable prospectus supplement, in denominations of $1,000 and any integral multiple thereof. The indenture provides that we may issue debt securities of a series in temporary or permanent global form and as book-entry securities that will be deposited with, or on behalf of, The Depository Trust Company, or DTC, or another depositary named by us and identified in the applicable prospectus supplement with respect to that series. To the extent the debt securities of a series are issued in global form and as book-entry, a description of terms relating to any book-entry securities will be set forth in the applicable prospectus supplement.

At the option of the holder, subject to the terms of the indenture and the limitations applicable to global securities described in the applicable prospectus supplement, the holder of the debt securities of any series can exchange the debt securities for other debt securities of the same series, in any authorized denomination and of like tenor and aggregate principal amount.

Subject to the terms of the indenture and the limitations applicable to global securities set forth in the applicable prospectus supplement, holders of the debt securities may present the debt securities for exchange or for registration of transfer, duly endorsed or with the form of transfer endorsed thereon duly executed if so required by us or the security registrar, at the office of the security registrar or at the office of any transfer agent designated by us for this purpose. Unless otherwise provided in the debt securities that the holder presents for transfer or exchange, we will impose no service charge for any registration of transfer or exchange, but we may require payment of any taxes or other governmental charges.

We will name in the applicable prospectus supplement the security registrar, and any transfer agent in addition to the security registrar, that we initially designate for any debt securities. We may at any time designate additional transfer agents or rescind the designation of any transfer agent or approve a change in the office through which any transfer agent acts, except that we will be required to maintain a transfer agent in each place of payment for the debt securities of each series.

If we elect to redeem the debt securities of any series, we will not be required to:

- issue, register the transfer of, or exchange any debt securities of that series during a period beginning at the opening of business 15 days before the day of mailing of a notice of redemption of any debt securities that may be selected for redemption and ending at the close of business on the day of the mailing; or
- register the transfer of or exchange any debt securities so selected for redemption, in whole or in part, except the unredeemed portion of any debt securities we are redeeming in part.

Information Concerning the Trustee

The trustee, other than during the occurrence and continuance of an event of default under an indenture, undertakes to perform only those duties as are specifically set forth in the applicable indenture. Upon an event of default under an indenture, the trustee must use the same degree of care as a prudent person would exercise or use in the conduct of his or her own affairs. Subject to this provision, the trustee is under no obligation to exercise any of the powers given it by the indenture at the request of any holder of debt securities unless it is offered reasonable security and indemnity against the costs, expenses and liabilities that it might incur.

Payment and Paying Agents

Unless we otherwise indicate in the applicable prospectus supplement, we will make payment of the interest on any debt securities on any interest payment date to the person in whose name the debt securities, or one or more predecessor securities, are registered at the close of business on the regular record date for the interest.

We will pay principal of and any premium and interest on the debt securities of a particular series at the office of the paying agents designated by us, except that unless we otherwise indicate in the applicable prospectus supplement, we will make interest payments by check that we will mail to the holder or by wire transfer to certain holders. Unless we otherwise indicate in the applicable prospectus supplement, we will designate the corporate trust office of the trustee as our sole paying agent for payments with respect to debt securities of each series. We will name in the applicable prospectus supplement any other paying agents that we initially designate for the debt securities of a particular series. We will maintain a paying agent in each place of payment for the debt securities of a particular series.

All money we pay to a paying agent or the trustee for the payment of the principal of or any premium or interest on any debt securities that remains unclaimed at the end of two years after such principal, premium or interest has become due and payable will be repaid to us, and the holder of the debt security thereafter may look only to us for payment thereof.

Governing Law

The indenture and the debt securities will be governed by and construed in accordance with the internal laws of the State of New York, except to the extent that the Trust Indenture Act of 1939 is applicable.

DESCRIPTION OF WARRANTS

The following description, together with the additional information we may include in any applicable prospectus supplements and in any related free writing prospectuses that we may authorize to be distributed to you, summarizes the material terms and provisions of the warrants that we may offer under this prospectus, which may consist of warrants to purchase common stock, preferred stock or debt securities and be issued in one or more series. Warrants may be offered independently or in combination with common stock, preferred stock or debt securities offered by any prospectus supplement. While the terms we have summarized below will apply generally to any warrants that we may offer under this prospectus, we will describe the particular terms of any series of warrants in more detail in the applicable prospectus supplement. The following description of warrants will apply to the warrants offered by this prospectus unless we provide otherwise in the applicable prospectus supplement. The applicable prospectus supplement for a particular series of warrants may specify different or additional terms.

We have filed forms of the warrant agreements and forms of warrant certificates containing the terms of the warrants that may be offered as exhibits to the registration statement of which this prospectus is a part. We will file as exhibits to the registration statement of which this prospectus is a part, or will incorporate by reference from reports that we file with the SEC, the form of warrant and/or the warrant agreement and warrant certificate, as applicable, that describe the terms of the particular series of warrants we are offering, and any supplemental agreements, before the issuance of such warrants. The following summaries of material terms and provisions of the warrants are subject to, and qualified in their entirety by reference to, all the provisions of the form of warrant and/or the warrant agreement and warrant certificate, as applicable, and any supplemental agreements applicable to a particular series of warrants that we may offer under this prospectus. We urge you to read the applicable prospectus supplement related to the particular series of warrants that we may offer under this prospectus, as well as any related free writing prospectuses, and the complete form of warrant and/or the warrant agreement and warrant certificate, as applicable, and any supplemental agreements, that contain the terms of the warrants.

General

We will describe in the applicable prospectus supplement the terms of the series of warrants being offered, including:

- the offering price and aggregate number of warrants offered;
- the currency for which the warrants may be purchased;
- if applicable, the designation and terms of the securities with which the warrants are issued and the number of warrants issued with each such security or each principal amount of such security;
- in the case of warrants to purchase debt securities, the principal amount of debt securities purchasable upon exercise of one warrant and the price at, and currency in which, this principal amount of debt securities may be purchased upon such exercise;
- in the case of warrants to purchase common stock or preferred stock, the number of shares of common stock or preferred stock, as the case may be, purchasable upon the exercise of one warrant and the price at which these shares may be purchased upon such exercise;
- the effect of any merger, consolidation, sale or other disposition of our business on the warrant agreements and the warrants;
- the terms of any rights to redeem or call the warrants;
- any provisions for changes to or adjustments in the exercise price or number of securities issuable upon exercise of the warrants;
- the dates on which the right to exercise the warrants will commence and expire;

- the manner in which the warrant agreements and warrants may be modified;
- a discussion of any material or special U.S. federal income tax considerations of holding or exercising the warrants;
- the terms of the securities issuable upon exercise of the warrants; and
- any other specific terms, preferences, rights or limitations of or restrictions on the warrants.

Before exercising their warrants, holders of warrants will not have any of the rights of holders of the securities purchasable upon such exercise, including:

- in the case of warrants to purchase debt securities, the right to receive payments of principal of, or premium, if any, or interest on, the debt securities purchasable upon exercise or to enforce covenants in the applicable indenture; or
- in the case of warrants to purchase common stock or preferred stock, the right to receive dividends, if any, or, payments upon our liquidation, dissolution or winding up or to exercise voting rights, if any.

Exercise of Warrants

Each warrant will entitle the holder to purchase the securities that we specify in the applicable prospectus supplement at the exercise price that we describe in the applicable prospectus supplement. The warrants may be exercised as set forth in the prospectus supplement relating to the warrants offered. Unless we otherwise specify in the applicable prospectus supplement, warrants may be exercised at any time up to the close of business on the expiration date set forth in the prospectus supplement relating to the warrants offered thereby. After the close of business on the expiration date, unexercised warrants will become void.

Upon receipt of payment and the warrant or warrant certificate, as applicable, properly completed and duly executed at the corporate trust office of the warrant agent, if any, or any other office, including ours, indicated in the prospectus supplement, we will, as soon as practicable, issue and deliver the securities purchasable upon such exercise. If less than all of the warrants (or the warrants represented by such warrant certificate) are exercised, a new warrant or a new warrant certificate, as applicable, will be issued for the remaining warrants.

Governing Law

Unless we otherwise specify in the applicable prospectus supplement, the warrants and any warrant agreements will be governed by and construed in accordance with the laws of the State of New York.

Enforceability of Rights by Holders of Warrants

Each warrant agent, if any, will act solely as our agent under the applicable warrant agreement and will not assume any obligation or relationship of agency or trust with any holder of any warrant. A single bank or trust company may act as warrant agent for more than one issue of warrants. A warrant agent will have no duty or responsibility in case of any default by us under the applicable warrant agreement or warrant, including any duty or responsibility to initiate any proceedings at law or otherwise, or to make any demand upon us. Any holder of a warrant may, without the consent of the related warrant agent or the holder of any other warrant, enforce by appropriate legal action its right to exercise, and receive the securities purchasable upon exercise of, its warrants.

CERTAIN PROVISIONS OF DELAWARE LAW, THE CERTIFICATE OF INCORPORATION AND BYLAWS

Limitations on Directors' Liability

Our amended and restated certificate of incorporation and our bylaws contain provisions indemnifying our directors and officers to the fullest extent permitted by law. In addition, as permitted by Delaware law, our amended and restated certificate of incorporation provides that no director will be liable to us or our stockholders for monetary damages for breach of certain fiduciary duties as a director. The effect of this provision is to restrict our rights and the rights of our stockholders in derivative suits to recover monetary damages against a director for breach of certain fiduciary duties as a director, except that a director will be personally liable for:

- the benefits to be derived from relationships with our collaborators;
- any breach of his or her duty of loyalty to the registrant or its stockholders;
- acts or omissions not in good faith which involve intentional misconduct or a knowing violation of law;
- the payment of dividends or the redemption or purchase of stock in violation of Delaware law; or
- any transaction from which the director derived an improper personal benefit.

This provision does not affect a director's liability under the federal securities laws.

To the extent that our directors, officers and controlling persons are indemnified under the provisions contained in our amended and restated certificate of incorporation, Delaware law or contractual arrangements against liabilities arising under the Securities Act, we have been advised that in the opinion of the Commission such indemnification is against public policy as expressed in the Securities Act, and is therefore unenforceable.

Provisions that May Have an Anti-Takeover Effect

Certain provisions set forth in our amended and restated certificate of incorporation, bylaws and in Delaware law, which are summarized below, are intended to enhance the likelihood of continuity and stability in the composition of our board of directors and in the policies formulated by our board of directors and to discourage certain types of transactions that may involve an actual or threatened change of control. In that regard, these provisions are designed to reduce our vulnerability to an unsolicited acquisition proposal. The provisions also are intended to discourage certain tactics that may be used in proxy fights. However, such provisions could have the effect of discouraging others from making tender offers for our shares and, as a consequence, they also may inhibit fluctuations in the market price of our common stock that could result from actual or rumored takeover attempts. Such provisions also may have the effect of preventing changes in our management.

Blank Check Preferred Stock. Our amended and restated certificate of incorporation contains provisions that permit our board of directors to issue, without any further vote or action by the stockholders, up to 30,000,000 shares of preferred stock in one or more series and, with respect to each such series, to fix the number of shares constituting the series and the designation of the series, the voting powers (if any) of the shares of the series, and the preferences and relative, participating, optional and other special rights, if any, and any qualifications, limitations or restrictions, of the shares of such series. As a result, our board of directors could authorize the issuance of shares of preferred stock with terms and conditions that could have the effect of delaying, deferring or preventing a transaction or a change in control that might involve a premium price for holders of the registrant's common stock or otherwise be in their best interest.

Special Meetings of Stockholders. Our bylaws provide that special meetings of stockholders may be called only by the board of directors. Stockholders are not permitted to call a special meeting of stockholders or to require that the board of directors call such a special meeting.

Delaware Takeover Statute.

We are subject to Section 203 of the Delaware General Corporation Law, or DGCL, which regulates acquisitions of some Delaware corporations. In general, Section 203 prohibits, with some exceptions, a Delaware corporation that is a public company from engaging in any "business combination" with any "interested stockholder" for a period of three years following the date that such stockholder became an interested stockholder, unless:

- prior to such date, the board of directors of the corporation approved either the business combination or the transaction that resulted in the stockholder becoming an interested stockholder;
- on consummation of the transaction that resulted in the stockholder becoming an interested stockholder, the interested stockholder owned at least 85% of the voting stock of the corporation outstanding at the time the transaction commenced, excluding for purposes of determining the number of shares outstanding those shares owned (x) by persons who are directors and also officers and (y) by employee stock plans in which employee participants do not have the right to determine confidentially whether shares held subject to the plan will be tendered in a tender or exchange offer; or
- on or subsequent to such date, the business combination is approved by the board of directors and authorized at an annual or special meeting of stockholders, and not by written consent, by the affirmative vote of at least 66 2/3% of the outstanding voting stock that is not owned by the interested stockholder.

Section 203 of the DGCL defines "business combination" to include:

- any merger or consolidation involving the corporation and the interested stockholder;
- any sale, transfer, pledge or other disposition of 10% or more of the assets of the corporation involving the interested stockholder;
- subject to certain exceptions, any transaction that results in the issuance or transfer by the corporation of any stock of the corporation to the interested stockholder;
- any transaction involving the corporation that has the effect of increasing the proportionate share of the stock of any class or series of the corporation beneficially owned by the interested stockholder; or
- the receipt by the interested stockholder of the benefit of any loans, advances, guarantees, pledges or other financial benefits provided by or through the corporation.

In general, Section 203 defines an "interested shareholder" as an entity or person beneficially owning 15% or more of the outstanding voting stock of the corporation and any entity or person affiliated with such entity or person.

LEGAL OWNERSHIP OF SECURITIES

We can issue securities in registered form or in the form of one or more global securities. We describe global securities in greater detail below. We refer to those persons who have securities registered in their own names on the books that we or any applicable trustee, depositary or warrant agent maintain for this purpose as the "holders" of those securities. These persons are the legal holders of the securities. We refer to those persons who, indirectly through others, own beneficial interests in securities that are not registered in their own names, as "indirect holders" of those securities. As we discuss below, indirect holders are not legal holders, and investors in securities issued in book-entry form or in street name will be indirect holders.

Book-Entry Holders

We may issue securities in book-entry form only, as we will specify in the applicable prospectus supplement. This means securities may be represented by one or more global securities registered in the name of a financial institution that holds them as depositary on behalf of other financial institutions that participate in the depositary's book-entry system. These participating institutions, which are referred to as participants, in turn, hold beneficial interests in the securities on behalf of themselves or their customers.

Only the person in whose name a security is registered is recognized as the holder of that security. Securities issued in global form will be registered in the name of the depositary or its participants. Consequently, for securities issued in global form, we will recognize only the depositary as the holder of the securities, and we will make all payments on the securities to the depositary. The depositary passes along the payments it receives to its participants, which in turn pass the payments along to their customers who are the beneficial owners. The depositary and its participants do so under agreements they have made with one another or with their customers; they are not obligated to do so under the terms of the securities.

As a result, investors in a global security will not own securities directly. Instead, they will own beneficial interests in a global security, through a bank, broker or other financial institution that participates in the depositary's book-entry system or holds an interest through a participant. As long as the securities are issued in global form, investors will be indirect holders, and not legal holders, of the securities.

Street Name Holders

We may terminate a global security or issue securities in non-global form. In these cases, investors may choose to hold their securities in their own names or in "street name." Securities held by an investor in street name would be registered in the name of a bank, broker or other financial institution that the investor chooses, and the investor would hold only a beneficial interest in those securities through an account he or she maintains at that institution.

For securities held in street name, we or any applicable trustee or depositary will recognize only the intermediary banks, brokers and other financial institutions in whose names the securities are registered as the holders of those securities, and we or any applicable trustee or depositary will make all payments on those securities to them. These institutions pass along the payments they receive to their customers who are the beneficial owners, but only because they agree to do so in their customer agreements or because they are legally required to do so. Investors who hold securities in street name will be indirect holders, not holders, of those securities.

Legal Holders

Our obligations, as well as the obligations of any applicable trustee and of any third parties employed by us or a trustee, run only to the legal holders of the securities. We do not have obligations to investors who hold beneficial interests in global securities, in street name or by any other indirect means. This will be the case whether an investor chooses to be an indirect holder of a security or has no choice because we are issuing the securities only in global form.

For example, once we make a payment or give a notice to the legal holder, we have no further responsibility for the payment or notice even if that legal holder is required, under agreements with its participants or customers or by law, to pass it along to the indirect holders but does not do so. Similarly, we may want to obtain the approval of the legal holders to amend an indenture, to relieve us of the consequences of a default or of our obligation to comply with a particular provision of the indenture or for other purposes. In such an event, we would seek approval only from the holders, and not the indirect holders, of the securities. Whether and how the legal holders contact the indirect holders is up to the legal holders.

Special Considerations for Indirect Holders

If you hold securities through a bank, broker or other financial institution, either in book-entry form or in street name, you should check with your own institution to find out:

- how it handles securities payments and notices;
- whether it imposes fees or charges;
- how it would handle a request for the holders' consent, if ever required;
- whether and how you can instruct it to send you securities registered in your own name so you can be a holder, if that is permitted in the future;
- how it would exercise rights under the securities if there were a default or other event triggering the need for holders to act to protect their interests; and
- if the securities are in book-entry form, how the depositary's rules and procedures will affect these matters.

Global Securities

A global security is a security that represents one or any other number of individual securities held by a depositary. Generally, all securities represented by the same global securities will have the same terms.

Each security issued in book-entry form will be represented by a global security that we issue to, deposit with and register in the name of a financial institution or its nominee that we select. The financial institution that we select for this purpose is called the depositary. Unless we specify otherwise in the applicable prospectus supplement, DTC will be the depositary for all securities issued in book-entry form.

A global security may not be transferred to or registered in the name of anyone other than the depositary, its nominee or a successor depositary, unless special termination situations arise. We describe those situations below under "Special Situations When a Global Security Will Be Terminated." As a result of these arrangements, the depositary, or its nominee, will be the sole registered owner and legal holder of all securities represented by a global security, and investors will be permitted to own only beneficial interests in a global security. Beneficial interests must be held by means of an account with a broker, bank or other financial institution that in turn has an account with the depositary or with another institution that does. Thus, an investor whose security is represented by a global security will not be a legal holder of the security, but only an indirect holder of a beneficial interest in the global security.

If the prospectus supplement for a particular security indicates that the security will be issued in global form only, then the security will be represented by a global security at all times unless and until the global security is terminated. If termination occurs, we may issue the securities through another book-entry clearing system or decide that the securities may no longer be held through any book-entry clearing system.

Special Considerations for Global Securities

The rights of an indirect holder relating to a global security will be governed by the account rules of the investor's financial institution and of the depositary, as well as general laws relating to securities transfers. We

do not recognize an indirect holder as a holder of securities and instead deal only with the depositary that holds the global security.

If securities are issued only in the form of a global security, an investor should be aware of the following:

- an investor cannot cause the securities to be registered in his or her name, and cannot obtain non-global certificates for his or her interest in the securities, except in the special situations we describe below;
- an investor will be an indirect holder and must look to his or her own bank, broker or other financial institution for payments on the securities and protection of his or her legal rights relating to the securities, as we describe above;
- an investor may not be able to sell interests in the securities to some insurance companies and to other institutions that are required by law to own their securities in non-book-entry form;
- an investor may not be able to pledge his or her interest in a global security in circumstances where certificates representing the securities must be delivered to the lender or other beneficiary of the pledge in order for the pledge to be effective;
- the depositary's policies, which may change from time to time, will govern payments, transfers, exchanges and other matters relating to an investor's interest in a global security;
- we and any applicable trustee have no responsibility for any aspect of the depositary's actions or for its records of ownership interests in a global security, nor do we or any applicable trustee supervise the depositary in any way;
- the depositary may, and we understand that DTC will, require that those who purchase and sell interests in a global security within its book-entry system use immediately available funds, and your bank, broker or other financial institution may require you to do so as well; and
- financial institutions that participate in the depositary's book-entry system, and through which an investor holds its interest in a global security, may also have their own policies affecting payments, notices and other matters relating to the securities.

There may be more than one financial intermediary in the chain of ownership for an investor. We do not monitor and are not responsible for the actions of any of those intermediaries.

Special Situations When a Global Security Will Be Terminated

In a few special situations described below, the global security will terminate and interests in it will be exchanged for physical certificates representing those interests. After that exchange, the choice of whether to hold securities directly or in street name will be up to the investor. Investors must consult their own banks, brokers or other financial institutions to find out how to have their interests in securities transferred to their own name, so that they will be direct holders. We have described the rights of holders and street name investors above.

Unless we provide otherwise in the applicable prospectus supplement, the global security will terminate when the following special situations occur:

- if the depositary notifies us that it is unwilling, unable or no longer qualified to continue as depositary for that global security and we do not appoint another institution to act as depositary within 90 days;
- if we notify any applicable trustee that we wish to terminate that global security; or
- if an event of default has occurred with regard to securities represented by that global security and has not been cured or waived.

The applicable prospectus supplement may also list additional situations for terminating a global security that would apply only to the particular series of securities covered by the applicable prospectus supplement. When a global security terminates, the depositary, and not we or any applicable trustee, is responsible for deciding the names of the institutions that will be the initial direct holders.

PLAN OF DISTRIBUTION

We may sell the securities from time to time pursuant to underwritten public offerings, negotiated transactions, block trades or a combination of these methods. We may sell the securities to or through underwriters or dealers, through agents, or directly to one or more purchasers. We may distribute securities from time to time in one or more transactions:

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

We may also sell equity securities covered by this registration statement in an "at the market offering" as defined in Rule 415 under the Securities Act. Such offering may be made into an existing trading market for such securities in transactions at other than a fixed price, either:

- on or through the facilities of Nasdaq or any other securities exchange or quotation or trading service on which such securities may be listed, quoted or traded at the time of sale; and/or
- other than on Nasdaq or such other securities exchanges or quotation or trading services.

Such at the market offerings, if any, may be conducted by underwriters acting as principal or agent.

A prospectus supplement or supplements (and any related free writing prospectus that we may authorize to be provided to you) will describe the terms of the offering of the securities, including, to the extent applicable:

- the name or names of any underwriters, dealers or agents, if any;
- the purchase price of the securities and the proceeds we will receive from the sale;
- any over-allotment options under which underwriters may purchase additional securities from us;
- any agency fees or underwriting discounts and other items constituting agents' or underwriters' compensation;
- any public offering price;
- any discounts or concessions allowed or reallowed or paid to dealers; and
- any securities exchange or market on which the securities may be listed.

Only underwriters named in the prospectus supplement are underwriters of the securities offered by the prospectus supplement.

If underwriters are used in the sale, they will acquire the securities for their own account and may resell the securities from time to time in one or more transactions at a fixed public offering price or at varying prices determined at the time of sale. The obligations of the underwriters to purchase the securities will be subject to the conditions set forth in the applicable underwriting agreement. We may offer the securities to the public through underwriting syndicates represented by managing underwriters or by underwriters without a syndicate. Subject to certain conditions, the underwriters will be obligated to purchase all of the securities offered by the prospectus supplement. Any public offering price and any discounts or concessions allowed or reallowed or paid to dealers may change from time to time. We may use underwriters with whom we have a material relationship. We will describe in the prospectus supplement, naming the underwriter, the nature of any such relationship.

We may sell securities directly or through agents we designate from time to time. We will name any agent involved in the offering and sale of securities, and we will describe any commissions we will pay the agent in the prospectus supplement. Unless the prospectus supplement states otherwise, our agent will act on a best-efforts basis for the period of its appointment.

We may authorize agents or underwriters to solicit offers by certain types of institutional investors to purchase securities from us at the public offering price set forth in the prospectus supplement pursuant to delayed delivery contracts providing for payment and delivery on a specified date in the future. We will describe the conditions to these contracts and the commissions we must pay for solicitation of these contracts in the prospectus supplement.

We may provide agents and underwriters with indemnification against civil liabilities related to this offering, including liabilities under the Securities Act, or contribution with respect to payments that the agents or underwriters may make with respect to these liabilities. Agents and underwriters may engage in transactions with, or perform services for, us in the ordinary course of business.

All securities we offer, other than common stock, will be new issues of securities with no established trading market. Any underwriters may make a market in these securities, but will not be obligated to do so and may discontinue any market making at any time without notice. We cannot guarantee the liquidity of the trading markets for any securities.

Any underwriter may engage in overallotment, stabilizing transactions, short covering transactions and penalty bids. Overallotment involves sales in excess of the offering size, which create a short position. Stabilizing transactions permit bids to purchase the underlying security so long as the stabilizing bids do not exceed a specified maximum. Short covering transactions involve purchases of the securities in the open market after the distribution is completed to cover short positions. Penalty bids permit the underwriters to reclaim a selling concession from a dealer when the securities originally sold by the dealer are purchased in a stabilizing or covering transaction to cover short positions. Those activities may cause the price of the securities to be higher than it would otherwise be. If commenced, the underwriters may discontinue any of the activities at any time. These transactions may be effected on any exchange or over-the-counter market or otherwise.

Any underwriters who are qualified market makers on Nasdaq may engage in passive market making transactions in the securities on Nasdaq in accordance with Rule 103 of Regulation M, during the business day prior to the pricing of the offering, before the commencement of offers or sales of the securities. Passive market makers must comply with applicable volume and price limitations and must be identified as passive market makers. In general, a passive market maker must display its bid at a price not in excess of the highest independent bid for such security; if all independent bids are lowered below the passive market maker’s bid, however, the passive market maker’s bid must then be lowered when certain purchase limits are exceeded. Passive market making may stabilize the market price of the securities at a level above that which might otherwise prevail in the open market and, if commenced, may be discontinued at any time.

LEGAL MATTERS

Unless otherwise indicated in the applicable prospectus supplement, certain legal matters in connection with the offering and the validity of the securities offered by this prospectus, and any supplement thereto, will be passed upon by Cooley LLP. Any underwriters will also be advised about the validity of the securities and other legal matters by their own counsel, which will be named in the prospectus supplement.

EXPERTS

The financial statements of ZIOPHARM Oncology, Inc. as of December 31, 2018 and 2017 and for each of the years in the three-year period ended December 31, 2018 and the effectiveness of internal control over financial reporting as of December 31, 2018, incorporated in these Prospectuses by reference from the ZIOPHARM Oncology, Inc. Annual Report on Form 10-K for the year ended December 31, 2018, have been audited by RSM US LLP, an independent registered public accounting firm, as stated in their report thereon (which report expresses an unqualified opinion) incorporated herein by reference, and have been incorporated in these Prospectuses and Registration Statement in reliance upon such report and upon the authority of such firm as experts in accounting and auditing.

WHERE YOU CAN FIND MORE INFORMATION

This prospectus is part of a registration statement on Form S-3 we filed with the SEC under the Securities Act. This prospectus does not contain all of the information set forth in the registration statement and the exhibits to the registration statement. For further information with respect to us and the securities we are offering under this prospectus, we refer you to the registration statement and the exhibits and schedules filed as a part of the registration statement. You should rely only on the information contained in this prospectus or incorporated by reference. We have not authorized anyone else to provide you with different information. We are not making an offer of these securities in any state where the offer is not permitted. You should not assume that the information in this prospectus is accurate as of any date other than the date on the front page of this prospectus, regardless of the time of delivery of this prospectus or any sale of the securities offered by this prospectus.

We file annual, quarterly and current reports, proxy statements and other information with the SEC. The SEC maintains a website that contains reports, proxy statements and other information regarding issuers that file electronically with the SEC, including us. The address of the SEC website is www.sec.gov.

We maintain a website at www.ziopharm.com. Information found on, or accessible through, our website is not a part of, and is not incorporated into, this prospectus, and you should not consider it part of this prospectus or part of any prospectus supplement.

INCORPORATION OF INFORMATION BY REFERENCE

The SEC allows us to “incorporate by reference” information into this prospectus, which means that we can disclose important information to you by referring you to another document filed separately with the SEC. The SEC file number for the documents incorporated by reference in this prospectus is 001-33038. The documents incorporated by reference into this prospectus contain important information that you should read about us.

The following documents are incorporated by reference into this document:

- our Annual Report on Form 10-K for the year ended December 31, 2018, filed with the SEC on March 5, 2019;

- the information specifically incorporated by reference into our Annual Report on Form 10-K for the year ended December 31, 2018 from our definitive proxy statement on Schedule 14A (other than information furnished rather than filed), which was filed with the SEC on April 29, 2019;
- our Quarterly Report on Form 10-Q for the fiscal quarter ended March 31, 2019, filed with the SEC on May 8, 2019;
- our Current Reports on Form 8-K filed with the SEC on January 10, 2019, February 4, 2019, April 29, 2019, May 28, 2019 and June 17, 2019 to the extent the information in such reports is filed and not furnished; and
- the description of our common stock set forth in the registration statement on Form 8-A registering our common stock under Section 12 of the Exchange Act, which was filed with the SEC on September 20, 2006, including any amendments or reports filed for purposes of updating such description.

We also incorporate by reference any future filings (other than current reports furnished under Item 2.02 or Item 7.01 of Form 8-K and exhibits filed on such form that are related to such items unless such Form 8-K expressly provides to the contrary) made with the SEC pursuant to Sections 13(a), 13(c), 14 or 15(d) of the Exchange Act, including those made after the date of the initial filing of the registration statement of which this prospectus is a part and prior to effectiveness of such registration statement, until we file a post-effective amendment that indicates the termination of the offering of the common stock made by this prospectus and will become a part of this prospectus from the date that such documents are filed with the SEC. Information in such future filings updates and supplements the information provided in this prospectus. Any statements in any such future filings will automatically be deemed to modify and supersede any information in any document we previously filed with the SEC that is incorporated or deemed to be incorporated herein by reference to the extent that statements in the later filed document modify or replace such earlier statements.

We will provide to each person, including any beneficial owner, to whom a prospectus is delivered, without charge upon written or oral request, a copy of any or all of the documents that are incorporated by reference into this prospectus but not delivered with the prospectus, including exhibits that are specifically incorporated by reference into such documents. You may request a copy of such documents at no cost, by writing or telephoning us at the following address or telephone number:

Ziopharm Oncology, Inc.
One First Avenue, Parris Building 34, Navy Yard Plaza
Boston, Massachusetts 02129
Attention: General Counsel
(617) 259-1970

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Shares

ZIOPHARM Oncology, Inc.

Common Stock

PROSPECTUS SUPPLEMENT

Sole Book-Running Manager

Jefferies

Lead Manager

Cantor

February , 2020