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Filed Pursuant to Rule 424(b)(5)
Registration No. 333-214392

PROSPECTUS SUPPLEMENT
(To Prospectus dated November 2, 2016)

3,870,000 Shares

Loxo Oncology, Inc.

Common Stock

$31.00 per share

We are selling 3,870,000 shares of our common stock pursuant to this prospectus supplement and the accompanying prospectus.

We have granted the underwriters an option for a period of 30 days to purchase up to 580,500 additional shares of our common stock.

Our common stock is quoted on The Nasdaq Global Market under the symbol "LOXO." On January 4 2017, the last reported sales price for our common stock was $32.69 per share.

We are an "emerging growth company" as defined in the Jumpstart Our Business Startups Act of 2012 and, as such, we may have elected to comply with certain reduced public company reporting requirements.

An investment in our common stock involves a high degree of risk. You should carefully consider the information under the heading "Risk Factors" beginning on page S-11 of this prospectus supplement and in the documents incorporated by reference into this prospectus supplement before investing in our securities.

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	$ 31.00	$ 119,970,000
Underwriting discount(1)	$ 1.86	$ 7,198,200
Proceeds, before expenses, to us	$ 29.14	$ 112,771,800

(1) See "Underwriting" beginning on page S-24 of this prospectus supplement for additional information regarding the compensation payable to the underwriters.

If the underwriters exercise the option in full, the total underwriting discounts and commissions payable by us will be $8.3 million, and the total proceeds to us, before expenses, will be $129.7 million.

The underwriters expect to deliver the shares to purchasers on or about January 10, 2017 through the book-entry facilities of The Depository Trust Company.

Joint Book-Running Managers

Morgan Stanley **Citigroup** **Cowen and Company**

Lead Manager

Stifel

Prospectus Supplement dated January 4, 2017

We have not, and the underwriters have not, authorized anyone to provide you with information different than that contained or incorporated by reference in this prospectus supplement, the accompanying prospectus or any free writing prospectus that we have authorized for use in connection with this offering. We take no responsibility for, and can provide no assurance as to the reliability of, any other information that others may give you. You should assume that the information appearing 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 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 information in the documents to which we have referred you in the sections of this prospectus supplement entitled "Where You Can Find More Information" and "Incorporation of Information by Reference."

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ABOUT THIS PROSPECTUS SUPPLEMENT

On November 2, 2016, we filed with the Securities and Exchange Commission, or SEC, a registration statement on Form S-3 (File No. 333-214392) utilizing a shelf registration process relating to the securities described in this prospectus supplement, which registration statement became effective on November 16, 2016. Under this shelf registration process, we may, from time to time, sell common stock and other securities, of which this offering is a part.

This document is in two parts. The first part is the prospectus supplement, including the documents incorporated by reference herein, which describes the specific terms of this offering and also adds to and updates the information contained in the accompanying prospectus and the documents incorporated by reference. The second part, the accompanying prospectus, including the documents incorporated by reference therein, provides more general information, some of which may not apply to this offering. Generally, when we refer to this prospectus, we are referring to both parts of this document combined. Before you invest, you should carefully read this prospectus supplement, the accompanying prospectus and the information incorporated by reference herein and therein, as well as the additional information described in this prospectus supplement under "Where You Can Find More Information." This prospectus supplement may add, update or change information contained in the accompanying prospectus. To the extent that any statement we make in this prospectus supplement is inconsistent with statements made in the accompanying prospectus or any documents incorporated by reference therein, the statements made in this prospectus supplement will be deemed to modify or supersede those made in the accompanying prospectus and such documents incorporated by reference therein.

We are offering to sell, and seeking offers to buy, shares of our common stock only in jurisdictions where offers and sales are permitted. The distribution of this prospectus supplement and the 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 must inform themselves about, and observe any restrictions relating to, the offering of the common stock and the distribution of this prospectus supplement outside the United States. This prospectus supplement does 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 by any person in any jurisdiction in which it is unlawful for such person to make such an offer or solicitation.

This prospectus supplement, the accompanying prospectus and the documents incorporated by reference herein and therein include trademarks, service marks and trade names owned by us or other companies. All trademarks, service marks and trade names included or incorporated by reference into this prospectus supplement or the accompanying prospectus are the property of their respective owners.

In this prospectus, unless the context otherwise requires, the terms "Loxo," the "Company," "we," "us," and "our" refer to Loxo Oncology, Inc., a Delaware corporation.

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PROSPECTUS SUPPLEMENT SUMMARY

This summary highlights selected information about us, this offering and information appearing elsewhere in this prospectus supplement, in the accompanying prospectus and in the documents incorporated by reference herein and therein. This summary is not complete and does not contain all the information you should consider before investing in our common stock pursuant to this prospectus supplement and the accompanying prospectus. Before making an investment decision, to fully understand this offering and its consequences to you, you should carefully read this entire prospectus supplement, the accompanying prospectus and the information incorporated by reference, including "Risk Factors," the financial statements, and related notes, and the other information that we incorporate by reference herein and therein.

Company Overview

Loxo Oncology is a biopharmaceutical company innovating the development of highly selective medicines for patients with genetically defined cancers. Our pipeline focuses on cancers that are uniquely dependent on single gene abnormalities, such that a single drug has the potential to treat the cancer with dramatic effect. We believe that the most selective, purpose-built medicines have the highest probability of maximally inhibiting the intended target, thereby delivering best-in-class disease control and safety. Our management team seeks out experienced industry partners, world-class scientific advisors and innovative clinical-regulatory approaches to deliver new cancer therapies to patients as quickly and efficiently as possible.

As genetic testing in cancer becomes more routine, we are learning that cancers arising in diverse sites in the body may share the same type of genetic alterations. Increasingly, tumors may be identified and treated according to their distinguishing genetic alterations, while in the past, the organ of origin was most important. Both research and clinical data suggest that some tumors, while having many identifiable genetic alterations, are primarily dependent on a single activated kinase for their proliferation and survival. This dependency, often referred to as oncogene addiction, renders such tumors highly susceptible to small molecule inhibitors targeting the relevant alteration.

We identify and prioritize our targets in two ways. First, we use reported clinical trial data to assess the response signals of drugs in development and identify those that show promise but also demonstrate drug-specific limitations such as poor absorption, poor distribution or unwanted side effects. Second, we evaluate academic research to uncover novel targets with emerging validation. Once the target is identified, we then employ advanced third-party technology to develop product candidates intended to have enhanced target engagement and specificity. We implement a stepwise approach to clinical development designed to reduce risk and identify response signals early in development. In early-stage trials we plan to evaluate our product candidates in well-defined patient populations and believe that this gives us a higher likelihood of demonstrating a clinical benefit. This approach allows for the possibility of rapid clinical development and expedited regulatory strategies. We intend to develop companion diagnostics when appropriate, with the help of technology partners, to identify patients whose tumors harbor relevant genetic alterations.

To build a pipeline of targeted therapeutics, we entered into a multi-target collaboration with Array BioPharma Inc., or Array, to leverage its expertise in building highly selective and potent kinase inhibitors. The collaboration was designed around a broad list of targets to give us the flexibility to prioritize the most promising of these targets for advancement into clinical development. We believe that this collaboration allows us to develop multiple targeted therapeutics in a rapid and capital-efficient manner. We retain worldwide commercial rights for all of our product candidates.

Larotrectinib

Overview. Larotrectinib, formerly referred to as LOXO-101, is an oral, selective inhibitor of the TRK family that we are developing for the treatment of tumors with TRK alterations. TRK has been

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implicated in diverse tumor types such as lung cancer, head and neck cancer, melanoma, colorectal cancer, sarcoma, and breast cancer. We selected larotrectinib from a portfolio of Array TRK inhibitors that had distinct chemical scaffolds and were initially developed to treat pain, a setting in which positive efficacy signals had been seen with antibodies targeting the TRK pathway. As a result of the initial focus on a pain indication, the TRK inhibitors were designed for both potency and specificity. In purified enzyme inhibition studies, larotrectinib has demonstrated potent inhibition activity against TRKA, TRKB and TRKC at low nanomolar concentration levels. These studies also demonstrated that larotrectinib was highly selective as it was not a strong inhibitor of any other tested kinase.

Similarly, in cells expressing these TRK receptors, larotrectinib also demonstrated potent inhibition activity at low nanomolar concentrations. We believe that potent and selective inhibition of the TRK pathway may provide clinical benefit in patients whose tumors have relevant TRK alterations. Given larotrectinib's specificity, we do not anticipate clinical activity in patients whose tumors are not driven by TRK.

TRK Biology. TRK plays important roles in neuronal development, including the growth and function of neuronal synapses, memory development and maintenance and the protection of neurons after ischemia or other injuries. TRK expression decreases after birth in most tissues and in adults expression is restricted primarily to cells of neural crest with a low level of expression under normal conditions. More recently, the role of TRK in non-neural tissues has also been recognized; these tissues include the kidney, prostate, B-lymphocytes, eosinophils, marrow-derived endothelial precursors (involving heart, muscle and ovary) and embryonic stem cells. Three high-affinity TRK receptors have been identified: TRKA, TRKB and TRKC. These proteins are encoded by the NTRK1, NTRK2 and NTRK3 genes, respectively.

Multiple downstream pathways believed to be important in cancer are stimulated by activated TRK receptors, including the PI3-kinase, phospholipase C-gamma, and MAP-kinase pathways. Drugs targeting some of these pathways have demonstrated clinical activity in the treatment of cancer.

The Role of TRK in Cancer. TRK has been widely implicated in multiple cancer types and research suggests that the genes that code TRK are frequently involved in fusion events, or the abnormal connection of two genes. Fusion events can result in pathologic activation of cellular growth and proliferation pathways. The first TRK fusion kinases that were discovered in solid tumors involved the NTRK1 gene in colon cancer. In 2002, fusion kinases involving NTRK3 were identified in secretory breast carcinoma, a rare subtype of breast cancer. More recently, research has uncovered multiple other instances of fusions involving the genes that code TRK. For example, scientists identified NTRK1 gene fusions as oncogenic in lung adenocarcinomas in 2013. We believe that the growing body of scientific literature suggesting the presence of NTRK fusions suggests a possible dependency for cellular proliferation and survival, or an oncogenic addictive role, across multiple cancers.

Larotrectinib Phase 1 Study. We are evaluating larotrectinib in a Phase 1 dose escalation trial in up to approximately 108 patients with advanced solid tumors refractory to standard therapy. The primary endpoints of this open label, multicenter, dose escalation trial include safety assessments, determining the maximum tolerated dose and identifying the appropriate dose for further clinical investigation. Secondary endpoints include pharmacokinetic assessments of orally administered larotrectinib, evaluation of tumor response and duration of response. Adult patients are eligible provided they meet our eligibility criteria, including (1) locally advanced or metastatic adult solid tumor that has progressed or was nonresponsive to available therapies and for which no standard or available curative therapy exists, (2) an ECOG score, which measures disease progression, of 0, 1 or 2, with life expectancy of at least 3 months and (3) adequate hematologic, hepatic and renal function. We began enrolling patients in our Phase 1 trial in May 2014. Additional patient cohorts may be enrolled in an expansion phase of this trial to better characterize safety and efficacy in patients with specific abnormalities in the NTRK genes or proteins. We reported interim data for this trial at the European

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Society for Medical Oncology (ESMO) Asia Congress in Singapore in December 2016. As of November 10, 2016, 59 patients with refractory solid tumors had been enrolled and treated with single agent larotrectinib, including eight patients with cancers harboring TRK fusions.

Larotrectinib Interim Phase 1 Safety Data. As of November 10, 2016, larotrectinib has been well tolerated in the 59 patients treated, including 34 patients at a dose of 100mg BID. Adverse events reported regardless of attribution to study drug are generally consistent with those previously presented. The most common adverse events, largely Grade 1 and 2, include fatigue (37 percent), dizziness (29 percent), anemia (25 percent) and dyspnea (25 percent). Grade 3 or 4 adverse events occurring in more than two patients included anemia, fatigue, increased liver enzymes, and dyspnea. No individual Grade 3 or 4 adverse events occurred in more than three patients treated at 100mg BID or more than five patients in the entire study population. Three patients have withdrawn from the study due to adverse events. The frequency of toxicities did not correlate with dose level. The maximum tolerated dose, or MTD, has not yet been defined.

Larotrectinib Interim Phase 1 Efficacy Data. As of November 10, 2016, 59 patients with refractory solid tumors had been enrolled and treated with single agent larotrectinib. This includes eight patients with cancers harboring TRK fusions, representing a broad range of tumor types, namely mammary analogue secretory cancer of the salivary glands (MASC, n=3), gastrointestinal stromal tumor (n=2), soft tissue sarcoma, thyroid carcinoma and non-small cell lung cancer. Seven patients with TRK fusion cancers were on study sufficiently long for an efficacy assessment, while an eighth TRK fusion patient had been recently enrolled and was not yet evaluated for response. Six of the seven efficacy evaluable patients achieved a confirmed partial response, as defined by standard RECIST v1.1 criteria. A seventh patient, as previously reported, demonstrated clear radiographic tumor regressions, including in the central nervous system, and remained on study as of November 10, 2016, but had not met the threshold required for a RECIST v1.1 response. All responders remained in response as of November 10, 2016, with one patient in cycle 22, one patient in cycle 19, one patient in cycle 18, two patients in cycle 15 and one patient in cycle 11. Each cycle is 28 days, or approximately one month.

All seven patients remain on study as of November 10, 2016. The eighth patient was recently enrolled and not yet evaluable for efficacy as of November 10, 2016, but also remains on study.

Larotrectinib Phase 2 Basket Study. In October 2015, we announced the initiation of our Phase 2 basket trial, a multicenter, international open label study in adult cancer patients whose tumors harbor TRK fusions, with the treatment of our first study subject. A basket trial is a type of clinical study that seeks to enroll cancer patients with a common genetic feature, in this case, a TRK fusion, as opposed to patients with a particular type of cancer. The larotrectinib Phase 2 basket trial is enrolling patients with TRK fusions into one of eight cohorts: non-small cell lung cancer, thyroid cancer, sarcoma, colorectal cancer, salivary gland cancer, biliary cancer, primary central nervous system tumors and all other solid tumor types. Available scientific evidence suggests that TRK fusions behave similarly across tumor types, but this approach allows for independent statistical analyses of each cohort for the purposes of evaluating efficacy or futility. The total size of the trial is not expected to exceed 151 patients. In order to meet the criteria for enrollment, patients must have received prior standard therapy appropriate for their tumor type and stage of disease, or in the opinion of the investigator, would be unlikely to tolerate or derive clinical benefit from appropriate standard of care therapy. During this trial, larotrectinib is administered orally as a single agent continuously in 28-day cycles. The 100 mg twice-daily dose, which was administered to five of the seven evaluable TRK fusion patients, has been selected for this trial. The primary endpoint of the trial is the overall response rate to larotrectinib, as measured by the proportion of subjects with best overall confirmed response of complete response or partial response by RECIST v1.1, or Response Assessment in Neuro-Oncology RANO, criteria, as appropriate. Secondary endpoints include duration of response, the proportion of subjects that have any tumor regression as a best response, progression-free survival, overall survival,

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safety and tolerability. We collaborate with the clinical, laboratory, and molecular pathology communities in both academia and industry to ensure that that TRK fusion patients and their treating physicians are alerted to the larotrectinib Phase 2 clinical trial, integrating trial recruitment into routine clinical practice.

Larotrectinib Inclusion in NCI-MATCH Study. In October 2015, we also announced that the independent committee of the National Cancer Institute-Molecular Analysis for Therapy Choice, or NCI-MATCH, clinical trial chose larotrectinib as the sole, dedicated treatment arm for patients with TRK gene fusions. The primary endpoint for NCI-MATCH is the objective response rate, defined as the percentage of patients whose tumors have a complete or partial response to treatment. The NCI-MATCH trial plans to initially enroll about 6,000 patients with tumor biopsies available for comprehensive genomic profiling and assign these patients to an appropriate targeted therapy arm based on the molecular abnormalities of each tumor. As part of the agreement between Loxo and NCI, Loxo will have access to data generated through this study which may be supportive as part of regulatory interactions. The TRK fusion arm of this study has yet to open and has not enrolled any patients. Results from this trial may, over time, provide supportive data in the context of the overall clinical development program, but are unlikely to constitute a primary or gating dataset that supports regulatory review.

Larotrectinib Phase 1/2 Pediatric Study. In December 2015, we announced the initiation of a Phase 1/2 multicenter, open-label trial of larotrectinib in pediatric patients with advanced solid or primary central nervous system (CNS) tumors, with the treatment of our first study subject. On April 19, 2016, the journal *Pediatric Blood and Cancer* published a manuscript co-authored with Nemours Children's Hospital, Northwestern University and St. Jude Children's Research Hospital, describing a confirmed RECIST v1.1 partial response in the first patient enrolled in the pediatric trial of larotrectinib. The 16-month-old female had infantile fibrosarcoma involving the neck, face, skull, mastoids and cervical vasculature. At the end of cycle 1 (day 28), imaging of the brain and neck showed tumor regression of more than 90 percent from baseline. Repeat scans at the end of cycle 2 showed a continued decrease in tumor volume. During the preparation of the manuscript, the patient was in study cycle 5, with a RECIST v1.1 confirmed partial response. The patient experienced no adverse events related to larotrectinib.

We plan to open as many as 15 clinical sites in the United States and enroll at least 36 patients. In the dose-escalation phase, larotrectinib is administered orally twice daily, with the initial starting dose level intended to match the pharmacokinetic exposures of the 100 mg twice daily dose that is currently being employed in the larotrectinib Phase 2 basket trial in adult patients. The actual dose for each patient will depend on the patient's body size and age. The trial utilizes a liquid formulation of larotrectinib designed specifically for pediatric patients unable to swallow capsules, though the capsule dosage form is available as an option as well. The primary objective of the trial is to explore the safety of larotrectinib. Secondary objectives include the characterization of pharmacokinetic properties, the identification of the maximum tolerated dose and/or the Phase 2 dose, a description of antitumor activity, and a description of pain and health related quality of life impact. Some pediatric cancers are pathognomonically defined by TRK fusions and others are highly enriched for the presence of TRK fusions. In line with our mission to enable clinical trial access to as many TRK fusion patients as possible, we view pediatric clinical development as an important forethought, not afterthought, in the clinical development plan for larotrectinib. We plan to present clinical data from the Phase 1/2 trial in pediatric patients in mid-2017.

Orphan Drug Status. In September 2015, we announced that the United States Food and Drug Administration, or the FDA, granted larotrectinib orphan drug designation for the treatment of soft tissue sarcoma.

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In January 2016, we announced that the European Commission designated larotrectinib as an orphan medicinal product for treatment of patients with soft tissue sarcoma.

Rare Pediatric Disease Designation. The FDA has granted rare pediatric disease designation to larotrectinib for the treatment of infantile fibrosarcoma, a rare pediatric cancer. The designation provides the opportunity for us to apply for a rare pediatric disease priority review voucher. Whether FDA grants us a priority review voucher at the time of drug approval will depend on the FDA's interpretation of the statute and guidance relevant to the program, and whether the population described in larotrectinib's first approved indication sufficiently encompasses the population covered by the rare pediatric disease designation or is broader than permitted under the statute and guidance to obtain a voucher. We estimate that there may be approximately 100 new cases of infantile fibrosarcoma per year in the United States.

Breakthrough Therapy Designation. In July 2016, the FDA granted Breakthrough Therapy Designation to larotrectinib "for the treatment of unresectable or metastatic solid tumors with NTRK-fusion proteins in adult and pediatric patients who require systemic therapy and who have either progressed following prior treatment or who have no acceptable alternative treatments." The larotrectinib Breakthrough Therapy Designation application, submitted approximately 60 days prior to designation receipt, included data from the ongoing Phase 1 dose-escalation study of larotrectinib in adult patients with advanced solid tumors, the ongoing Phase 1/2 pediatric study of larotrectinib in patients with advanced solid tumors or primary CNS tumors, and the ongoing Phase 2 basket trial of larotrectinib in adult cancer patients whose tumors harbor TRK fusions.

Clinical Development. As of December 19, 2016, our larotrectinib program was approximately 85% enrolled to goal, and we plan to complete enrollment for the primary efficacy analysis in early 2017. We expect that the efficacy and safety database sizes for larotrectinib will be within precedents set by prior targeted therapy drug approvals in oncology. The larotrectinib clinical trials will remain open to continue long-term follow-up of enrolled patients and provide a mechanism for continued drug access to newly identified patients through trial enrollment during regulatory interactions. We expect to be in a position in the second half of 2017 to report top-line data that, consistent with discussions with FDA, we anticipate will serve as the basis of the New Drug Application, or NDA, dataset. We expect to submit an NDA in late 2017 or early 2018 after a pre-NDA meeting with FDA, and a European Marketing Authorisation Application, or MAA, in 2018. We intend to submit for the following indication: "for the treatment of unresectable or metastatic solid tumors with NTRK-fusion proteins in adult and pediatric patients who require systemic therapy and who have either progressed following prior treatment or who have no acceptable alternative treatments." However, we can make no assurances that the FDA will grant us approval for the indication that we are seeking, or at all.

Commercial Opportunity. As we approach an NDA submission, we have learned more about the patient opportunity for larotrectinib. In addition to evidence from the literature summarized in the below table, we have worked closely with tumor banks, third party labs, and various assay technology partners to better understand TRK fusion frequency and how to improve testing sensitivity.

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Frequency of NTRK Fusions in Multiple Tumor Types

Gene Fusion	Cancer	Estimated Frequency <5%	5 - 25%	>75%
NTRK1	Papillary thyroid cancer		✓	
NTRK1	Spitz neoplasms nevi		✓	
NTRK1	Glioblastoma	✓		
NTRK1	Intrahepatic cholangiocarcinoma	✓		
NTRK1	Lung large cell neuroendocrine cancer	✓		
NTRK1	Sarcoma	✓		
NTRK2	Astrocytoma	✓		
NTRK3	Mammary analogue secretory carcinoma (MASC) of the salivary glands			✓
NTRK3	Secretory breast carcinoma			✓
NTRK3	Infantile fibrosarcoma			✓
NTRK3	Congenital mesoblastic nephroma		✓	
NTRK3	Papillary thyroid cancer (post-radiation exposure)		✓	
NTRK3	Acute myeloid leukemia	✓		
NTRK3	Breast invasive carcinoma	✓		
NTRK3	Gastrointestinal stromal tumors	✓		
NTRK3	Papillary thyroid cancer	✓		
NTRK3	Skin cutaneous melanoma	✓		
NTRK1/2	Lung adenocarcinoma	✓		
NTRK1/3	Colorectal cancer	✓		
NTRK2/3	Brain low-grade glioma	✓		
NTRK2/3	Head and neck squamous cell carcinoma	✓		
NTRK1/2/3	Pontine glioma		✓	

Our work suggests that in the United States, there are 1,500 to 5,000 late-line eligible patients each year. We also believe there are similar numbers of patients in the large European countries and Japan relative to those population sizes, as has been shown for other targeted therapies.

As we bring larotrectinib toward a potential commercial launch, it is crucial to ensure widespread adoption of sensitive diagnostic testing. The diagnostics that are being used today in clinical practice continue to improve in terms of technology and patient access—these two variables are key to finding the 1,500 to 5,000 patients who we believe exist each year. Our pre-launch preparations are highly focused on diagnostics and the pathology community.

Preclinical Product Pipeline

We are working on several pipeline programs in conjunction with our collaboration with Array.

LOXO-195

Acquired resistance to targeted therapies has proven to be an important component of long-term cancer care and targeted therapy drug development. In anticipation of potential resistance to larotrectinib, and in light of recent published literature regarding emerging mechanisms of resistance to TRK inhibition, we are developing our next-generation selective TRK inhibitor, LOXO-195, which is capable of addressing potential mechanisms of acquired resistance that may emerge in patients receiving larotrectinib or multikinase inhibitors with anti-TRK activity. With the LOXO-195 program, we believe we have an opportunity to strengthen our leadership position in the field of TRK inhibition and clinically extend the duration of disease control for patients with TRK-driven cancers.

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We presented preclinical data at the EORTC-NCI-AACR Molecular Targets and Cancer Therapeutics Symposium in December 2016 in Munich, Germany on our LOXO-195 preclinical program. LOXO-195 demonstrated potent and selective inhibition of TRK, and also all of the predicted resistance mutations reported in recent literature to date. LOXO-195 also exhibited favorable preclinical in vivo properties in relevant in vivo models of TRK acquired resistance.

We expect to submit an Investigational New Drug, or IND, application prior to initiating a LOXO-195 Phase 1 study in mid-2017. Initial clinical data may be available for this program as early as the end of 2017.

LOXO-292

We have identified our Rearranged during Transfection, or RET, program as the one most likely to deliver our next IND candidate. RET is a tyrosine kinase receptor that binds the glial cell line-derived neurotrophic factor (GDNF) ligand family and contributes to the development of the nervous system and kidneys. Activating fusions and mutations in RET have been identified across a range of cancer types, including lung, thyroid, breast and colon cancers. There are multiple peer-reviewed articles of patients with RET gene alterations demonstrating preliminary anti-tumor activity in experimental trials of kinase inhibitors with anti-RET activity. We are designing a highly specific RET inhibitor that is intended to optimize on-target potency for RET fusions, activating mutations, and anticipated resistance mutations.

RET fusions account for approximately 2% of non-small cell lung cancer. RET fusions also account for 10-20% of papillary thyroid cancer, and may be found in other tumors such as colon cancer, where prevalence is not well understood. RET mutations account for approximately 60% of medullary thyroid cancer. In lung and thyroid cancers, there are approximately 5,000 late-line eligible patients per year in the United States.

We presented preclinical data at the EORTC-NCI-AACR Molecular Targets and Cancer Therapeutics Symposium in December 2016 in Munich, Germany on our LOXO-292 preclinical program. LOXO-292 demonstrated RET potency in enzyme and cellular assays with minimal activity against highly related kinases and other off-targets. Preclinically, in vivo, LOXO-292 demonstrated its ability to drive tumor regresions in relevant RET-driven models, while having minimal effect on body weight, a proxy for toxicity. LOXO-292 also demonstrated potency against many anticipated mechanisms of acquired resistance, both in vitro and in vivo.

We expect to submit an IND prior to initiating a LOXO-292 Phase 1 study in early 2017. Initial clinical data may be available for this program as early as the end of 2017.

FGFR

We are also designing an FGFR1-sparing FGFR inhibitor that has the potential to avoid many of the side effects that have been endemic to the FGFR class. The FGFR family of receptors consists of four isoforms with tyrosine kinase domains, numbered one through four (1-4), which play important roles in embryonic development and adult angiogenesis, hormone regulation, and renal function. Fusions, point mutations, and gene amplifications in individual isoforms of the FGFR family have been associated with distinct cancer types in patients, and preliminary anti-tumor activity has been demonstrated in genitourinary, lung, and breast cancers in experimental trials of kinase inhibitors with anti-FGFR activity. However, most small molecule FGFR inhibitors are functionally equipotent against isoforms FGFR1, FGFR2 and FGFR3, and are associated with metabolic and systemic toxicities that limit dose, duration of therapy and target engagement.

We presented preclinical data at the AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics meeting in November 2015 in Boston, MA on our FGFR preclinical

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program. Data for our potent and selective FGFR inhibitor show that it spared FGFR1 and other related kinases and possesses high oral bioavailability and favorable PK properties in animal models.

Recent Financial Information

We have not finalized our consolidated financial statements for the period ended December 31, 2016. Based on our current estimates, as of December 31, 2016, we had approximately $141.7 million in cash, cash equivalents and investments. The actual amounts that we report will be subject to our financial closing procedures and any final adjustments that may be made prior to the time our financial results for the period ended December 31, 2016, are finalized.

Corporate Information

We were incorporated in Delaware in 2013 as Loxo Oncology, Inc. Our principal executive offices are located at 281 Tresser Blvd., 9th Floor, Stamford, CT, 06901, and our telephone number is (203) 653-3880. We have research and development operations and corporate offices in South San Francisco, CA and Stamford, CT.

JOBS Act

We are an "emerging growth company" as defined in the Jumpstart Our Business Startups Act of 2012, or the JOBS Act. We will remain an emerging growth company until the earlier of the last day of the fiscal year following the fifth anniversary of the completion of our initial public offering in August 2014, the last day of the fiscal year in which we have total annual gross revenue of at least $1.0 billion, the date on which we are deemed to be a large accelerated filer (this means that we have been public for at least 12 months, have filed at least one annual report and the market value of our common stock that is held by non-affiliates exceeds $700 million as of the end of the second quarter of that fiscal year), or the date on which we have issued more than $1.0 billion in nonconvertible debt securities during the prior three-year period.

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THE OFFERING

Common stock offered by us	3,870,000 shares
Common stock to be outstanding after this offering	25,548,051 shares
Option to purchase additional shares	We have granted the underwriters an option for a period of 30 days to purchase an additional 580,500 shares of common stock.
Public offering price	$31.00 per share
Use of proceeds	We intend to use the net proceeds from this offering for early commercialization activities for larotrectinib, new and ongoing research and development activities, and general corporate purposes, which may include increased working capital, acquisitions or investments in businesses, products or technologies, and capital expenditures. See "Use of Proceeds."
Risk factors	See "Risk Factors" for a discussion of factors that you should read and consider before investing in our securities.
NASDAQ Global Market symbol	LOXO

Entities affiliated with certain of our affiliates have agreed to purchase an aggregate of approximately $5.0 million of our common stock in this offering at the public offering price. Any shares purchased by investors that are our affiliates will be subject to lock-up restrictions described in the section of this prospectus entitled "Underwriting."

The number of shares of our common stock to be outstanding immediately after this offering as shown above is based on 21,678,051 shares outstanding as of September 30, 2016 and excludes:

- 2,297,494 shares of common stock issuable upon exercise of outstanding options as of September 30, 2016, with a weighted-average exercise price of $12.94 per share;
- 1,067,984 shares of common stock reserved for future issuance under our 2014 Equity Incentive Plan as of September 30, 2016;
- 540,792 shares of common stock issuable upon exercise of outstanding options granted after September 30, 2016, with a weighted average exercise price of $25.88 per share;
- 650,437 additional shares of common stock reserved for future issuance under our 2014 Equity Incentive Plan as of January 1, 2017; and
- 149,600 shares of common stock reserved for future issuance under our 2014 Employee Stock Purchase Plan as of September 30, 2016.

Except as otherwise indicated, all information in this prospectus supplement assumes no exercise of the outstanding options described above and no exercise of the underwriters' option to purchase additional shares of common stock.

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RISK FACTORS

An investment in our securities involves a high degree of risk. Prior to making a decision about investing in our securities, you should carefully consider the risk factors described below together with all of the risks, uncertainties and assumptions discussed under Part II, Item 1A, "Risk Factors," in our Quarterly Report on Form 10-Q for the quarter ended September 30, 2016, which is incorporated herein by reference, and may be amended, supplemented or superseded from time to time by other reports we file with the SEC in the future. If any of the risks incorporated by reference or set forth below occurs, our business, operations and financial condition could suffer significantly. As a result, you could lose some or all of your investment in our common stock. The risks and uncertainties we have described are not the only ones we face. Additional risks and uncertainties not presently known to us or that we currently deem immaterial may also affect our business, operations and financial condition, or cause the value of our common stock to decline.

Our 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. You will be relying on the judgment of our management concerning these uses and you will not have the opportunity, as part of your investment decision, to assess whether the proceeds are being used appropriately. The failure of our management to apply these funds effectively could result in unfavorable returns and uncertainty about our prospects, each of which could cause the price of our common stock to decline.

If you purchase shares of common stock sold in this offering you will experience immediate and substantial dilution in your investment. You will experience further dilution if we issue additional equity securities in the future.

Since the price per share of our common stock being offered is substantially higher than the net tangible book value per share of our common stock, you will suffer substantial dilution with respect to the net tangible book value of the shares of common stock you purchase in this offering. Based on a public offering price of $31.00 per share and our net tangible book value as of September 30, 2016, if you purchase shares of common stock in this offering, you will suffer immediate and substantial dilution of $20.54 per share with respect to the net tangible book value of the common stock. See "Dilution" for a more detailed discussion of the dilution you will incur if you purchase shares of common stock in this offering.

In addition, we have a significant number of stock options outstanding, and may also choose to issue additional common stock, or securities convertible into or exchangeable for common stock, in the future. In the event that the outstanding options are exercised, or that we make additional issuances of common stock or other convertible or exchangeable securities, you could experience additional dilution.

Future sales of a substantial number of shares of our common stock by our existing stockholders could cause our stock price to decline.

The market price of our common stock could decline as a result of sales of substantial amounts of our common stock in the public market after the closing of this offering, or the perception that these sales could occur. For example, certain of our stockholders possess rights with respect to the registration of their shares under the Securities Act of 1933, as amended, or the Securities Act. Registration of these shares under the Securities Act would result in the shares becoming freely tradable without restriction under the Securities Act.

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In addition, we have a significant number of stock options outstanding. If a substantial number of shares of common stock underlying these options are sold, or if it is perceived that they will be sold, in the public market, the trading price of our common stock could decline.

The FDA has granted rare pediatric disease designation to larotrectinib for the treatment of infantile fibrosarcoma; however, an NDA for larotrectinib may not meet the eligibility criteria for a priority review voucher upon approval.

The FDA has granted rare pediatric disease designation to larotrectinib for the treatment of infantile fibrosarcoma, a rare pediatric cancer under section 529(d) of the Federal Food, Drug, and Cosmetic Act, or FDC Act. Designation of a drug as a drug for a rare pediatric disease does not guarantee that an NDA for such drug will meet the eligibility criteria for a rare pediatric disease priority review voucher at the time the application is approved. Under the FDC Act, we will need to request a rare pediatric disease priority review voucher in our original NDA for larotrectinib. The FDA may determine that an NDA for larotrectinib does not meet the eligibility criteria for a priority review voucher upon approval, including for the following reasons:

- infantile fibrosarcoma no longer meets the definition of rare pediatric disease;
- the NDA contains an active ingredient (including any ester or salt of the active ingredient) that has been previously approved in an NDA;
- the NDA is not deemed eligible for priority review;
- the NDA does not rely on clinical data derived from studies examining a pediatric population and dosages of the drug intended for that population (i.e., if the NDA does not contain sufficient clinical data to allow for adequate labeling for use by the full range of affected pediatric patients); or
- the NDA seeks approval for a different adult indication than the rare pediatric disease (for example, if the FDA were to determine that the current larotrectinib breakthrough therapy designation indication that includes adult and pediatric patients is a different indication than the infantile fibrosarcoma indication).

The authority for the FDA to award rare pediatric disease priority review vouchers for drugs that have received rare pediatric disease designation prior to September 30, 2020 currently expires on September 30, 2022. If the NDA for larotrectinib is not approved prior to September 30, 2022 for any reason, regardless of whether it meets the criteria for a rare pediatric disease priority review voucher, it will not be eligible for a priority review voucher. However, it is also possible the authority for FDA to award rare pediatric disease priority review vouchers will be further extended through Federal lawmaking.

Investors should not place undue reliance on the results of preclinical experiments or our ongoing Phase 1 clinical trial since they are not necessarily predictive of the results that will form the basis of our global regulatory approval packages, and larotrectinib may not receive regulatory approval.

In an ongoing Phase 1 clinical trial, larotrectinib has demonstrated encouraging preliminary safety and efficacy. As of the November 10, 2016 data cutoff, 59 patients with refractory solid tumors had been enrolled and treated with single agent larotrectinib, including eight patients with cancers harboring TRK fusions. Larotrectinib was well tolerated at doses that include and exceed the recommended Phase 2 dose of 100 mg BID. A maximum tolerated dose, or MTD, had not been defined. The majority of adverse events reported by the investigators were mild to moderate. The most common adverse events, largely Grade 1 and 2, include fatigue (37 percent), dizziness (29 percent), anemia (25 percent) and dyspnea (25 percent). Grade 3 or 4 adverse events occurring in more than two patients included anemia, fatigue, increased liver enzymes, and dyspnea. No individual Grade 3 or 4

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adverse events occurred in more than three patients treated at 100mg BID or more than five patients in the entire study population. Three patients have withdrawn from the study due to adverse events. Seven patients with TRK fusion cancers were on study sufficiently long for an efficacy assessment, while an eighth TRK fusion patient had been recently enrolled and was not yet evaluated for response. Six of the seven efficacy evaluable patients achieved a confirmed partial response, as defined by standard RECIST v1.1 criteria. Durability of response was also encouraging, as all responders remained in response. However, investors should not place undue reliance on the results from completed preclinical studies or data from our ongoing Phase 1 clinical trial since they do not ensure that other clinical trial data will be comparable, in terms of safety, overall response rate, or ORR, durability of response, or DOR, or other factors the FDA and other regulators will consider in determining whether to approve an NDA for larotrectinib.

The final dataset, upon which global regulatory decisions will be based, will differ from the datasets previously disclosed. Potential reasons for these differences include, but are not limited to:

- not all patients may demonstrate tumor regression, experience tumor regression that meets the measurement thresholds required under RECIST v1.1 for a partial response, or remain on study long enough for an initial or confirmatory response assessment;

- patients may discontinue larotrectinib treatment for a number of reasons, including an adverse event, tumor progression following a response, or a lack of tumor regression or clinical benefit and . discontinuations will impact larotrectinib's reported duration of therapy and DOR;

- additional time and patient accrual provide new opportunities to capture new adverse events and further characterize the ORR and DOR;

- for a final calculation of ORR and DOR, patients in the larotrectinib clinical trials will require independent radiology reviews, pursuant to which a new set of radiologists, not affiliated with the trial investigators, apply RECIST v1.1 measurements and readings to the study patients' primary radiology images—we expect, as is generally the case, that the ORR and DOR calculated based on the readings of the trial sites will differ from the ORR and DOR calculated during the independent radiology review process;

- patient accrual beyond the disclosed data will include study subjects with additional tumor types harboring TRK fusions, pediatric patients, and subjects with varying prior therapies and thus, the inclusion of these subpopulations in the final dataset may alter the characterization of larotrectinib's overall safety, ORR and DOR; and

- the precise composition of the final dataset is subject to additional regulatory feedback, which is expected closer to the time of an NDA, or equivalent, and the advice may vary by regulatory authority.

As a result, the final efficacy and safety datasets for larotrectinib have not been fully populated or established, and are expected to differ from any interim dataset publicly disclosed. Moreover, regulatory approvals will be based on the final efficacy and safety databases, and as such, we can give no assurance that larotrectnib will receive regulatory approval.

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FORWARD-LOOKING STATEMENTS

This prospectus supplement and the accompanying prospectus and the documents incorporated herein by reference contain "forward-looking statements" within the meaning of the Private Securities Litigation Reform Act of 1995. These forward-looking statements involve a number of risks and uncertainties. We caution readers that any forward-looking statement is not a guarantee of future performance and that actual results could differ materially from those contained in the forward-looking statement.

These statements are based on current expectations of future events. Such statements include, but are not limited to:

- our plans to develop and commercialize targeted therapeutics for patients with genetically defined cancers;
- our ongoing and planned clinical trials, including the timing of anticipated results;
- our ability to obtain funding for operations, including funding necessary to complete the clinical trials of larotrectinib and finance discovery and development of other product candidates;
- the timing of and our ability to obtain and maintain regulatory approvals for our product candidates;
- our ability to develop and obtain FDA approval of, or contract with a third party to develop and obtain FDA approval of a companion diagnostic;
- the rate and degree of market acceptance and clinical utility of our products;
- our ability to attract and retain collaborators with preclinical development expertise;
- our collaboration with Array;
- our commercialization, marketing and manufacturing capabilities and strategy;
- regulatory developments in the United States and foreign countries;
- our intellectual property position;
- the continued involvement of members of our Scientific Advisory Board and other key scientific or management personnel;
- our expectations regarding the period during which we qualify as an emerging growth company under the JOBS Act;
- our use of the proceeds from this offering;
- our ability to identify additional products or product candidates with significant commercial potential that are consistent with our commercial objectives; and
- our estimates regarding expenses, future revenue, capital requirements and needs for additional financing.

You can find many of these statements by looking for words like "believes," "expects," "anticipates," "estimates," "may," "might," "should," "will," "could," "plan," "intend," "project," "seek" or similar expressions in this prospectus supplement and the accompanying prospectus or in the documents incorporated by reference into this prospectus supplement and accompanying prospectus. We intend that such forward-looking statements be subject to the safe harbors created thereby.

These forward-looking statements are based on the current beliefs and expectations of our management and are subject to significant risks and uncertainties. If underlying assumptions prove inaccurate or unknown risks or uncertainties materialize, actual results may differ materially from

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current expectations and projections. Factors that might cause such a difference include those discussed under the section titled "Risk Factors" and elsewhere in this prospectus supplement and the accompanying prospectus and the documents incorporated by reference into this prospectus supplement or the accompanying prospectus. You are cautioned not to place undue reliance on these forward-looking statements, which speak only as of the date made.

All subsequent written or oral forward-looking statements attributable to us or any person acting on our behalf are expressly qualified in their entirety by the cautionary statements contained or referred to in this section. We do not undertake any obligation to release publicly any revisions to these forward-looking statements to reflect events or circumstances after the date of this prospectus or to reflect the occurrence of unanticipated events, except as may be required under applicable U.S. securities law. If we do update one or more forward-looking statements, no inference should be drawn that we will make additional updates with respect to those or other forward-looking statements.

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USE OF PROCEEDS

At the public offering price of $31.00 per share, we estimate that the net proceeds of this offering, after deducting underwriting discounts and commissions and estimated offering expenses, will be approximately $112.4 million, or $129.3 million if the underwriters' option to purchase additional shares is exercised in full. We cannot assure you that this offering will be completed.

We intend to use the net proceeds from the sale of common stock in this offering for early commercialization activities for larotrectinib, new and ongoing research and development activities, and general corporate purposes, which may include increased working capital, acquisitions or investments in businesses, products or technologies, and capital expenditures. As of the date of this prospectus supplement, we cannot specify with certainty any or all of the particular uses for the net proceeds to us from this offering. We also cannot estimate precisely the allocation of the net proceeds from this offering among these uses. The occurrence of unforeseen events or changed business conditions could result in the application of the net proceeds from this offering in a manner other than as described in this prospectus supplement. As a result, our management will retain broad discretion over the allocation of the net proceeds from this offering. Pending application of the proceeds of sale of the securities, we intend to invest the net proceeds of the sale in short-term, investment-grade, interest-bearing instruments.

PRICE RANGE OF COMMON STOCK

Our common stock has been quoted on The NASDAQ Global Market under the symbol "LOXO" since our initial public offering in July 2014. The following table sets forth, for the periods indicated, the reported high and low closing sales prices per share of our common stock as reported by The NASDAQ Global Market:

	High	Low
Fiscal Year ended December 31, 2015		
First Fiscal Quarter	$ 14.39	$ 10.05
Second Fiscal Quarter	$ 20.30	$ 10.89
Third Fiscal Quarter	$ 22.83	$ 15.78
Fourth Fiscal Quarter	$ 34.10	$ 17.72
Fiscal Year ended December 31, 2016		
First Fiscal Quarter	$ 27.95	$ 16.78
Second Fiscal Quarter	$ 28.64	$ 22.00
Third Fiscal Quarter	$ 30.09	$ 23.14
Fourth Fiscal Quarter	$ 34.97	$ 17.73
Fiscal Year ending December 31, 2017		
First Fiscal Quarter (through January 4, 2017)	$ 32.69	$ 31.05

The last reported sale price for our common stock on January 4, 2017 was $32.69 per share.

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DIVIDEND POLICY

We have never declared or paid cash dividends on our capital stock. We currently intend to retain any future earnings for use in the operation of our business and do not intend to declare or pay any cash dividends in the foreseeable future. Any further determination to pay dividends on our capital stock will be at the discretion of our board of directors, subject to applicable laws, and will depend on our financial condition, results of operations, capital requirements, general business conditions and other factors that our board of directors considers relevant. In addition, we may in the future enter into loan agreements that restrict our ability to pay dividends.

DILUTION

If you invest in our common stock, your interest will be diluted to the extent of the difference between the public offering price per share of our common stock and the as adjusted net tangible book value per share of our common stock immediately after this offering.

Our net tangible book value as of September 30, 2016 was approximately $154.8 million, or $7.14 per share. Net tangible book value per share is determined by dividing our total tangible assets, less total liabilities, by the number of shares of our common stock outstanding as of September 30, 2016. Dilution with respect to net tangible book value per share represents the difference between the amount per share paid by purchasers of shares of common stock in this offering and the net tangible book value per share of our common stock immediately after this offering.

After giving effect to the sale of 3,870,000 shares of our common stock at the public offering price of $31.00 per share, and after deducting estimated underwriting discounts and commissions and estimated offering expenses, our as adjusted net tangible book value as of September 30, 2016 would have been approximately $267.2 million, or $10.46 per share. This represents an immediate increase in net tangible book value of $3.32 per share to existing stockholders and immediate dilution of $20.54 per share to investors purchasing our common stock in this offering at the public offering price. The following table illustrates this dilution on a per share basis:

Public offering price per share		$ 31.00
Net tangible book value per share as of September 30, 2016	$ 7.14	
Increase in net tangible book value per share attributable to investors purchasing our common stock in this offering	3.32	
As adjusted net tangible book value per share after this offering		10.46
Dilution per share to investors purchasing our common stock in this offering		$ 20.54

If the underwriters exercise their option to purchase 580,500 additional shares in full, the as adjusted net tangible book value per share of our common stock after giving effect to this offering would be $10.87 per share, and the dilution in net tangible book value per share to investors purchasing common stock in this offering would be $20.13 per share.

The table and discussion above are based on 21,678,051 shares outstanding as of September 30, 2016 and excludes:

- 2,297,494 shares of common stock issuable upon exercise of outstanding options as of September 30, 2016, with a weighted-average exercise price of $12.94 per share;
- 1,067,984 shares of common stock reserved for future issuance under our 2014 Equity Incentive Plan as of September 30, 2016;
- 540,792 shares of common stock issuable upon exercise of outstanding options granted after September 30, 2016, with a weighted average exercise price of $25.88 per share;

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- 650,437 additional shares of common stock reserved for future issuance under our 2014 Equity Incentive Plan as of January 1, 2017; and

- 149,600 shares of common stock reserved for future issuance under our 2014 Employee Stock Purchase Plan as of September 30, 2016.

To the extent that outstanding options have been or may be exercised or other shares are issued, investors purchasing our common stock in this offering may experience further dilution. In addition, we may choose to issue additional common stock, or securities convertible into or exchangeable for common stock, in the future. The issuance of these securities could result in further dilution for investors purchasing our common stock in this offering.

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MATERIAL UNITED STATES FEDERAL INCOME TAX CONSEQUENCES FOR NON-U.S. HOLDERS OF OUR COMMON STOCK

The following summary describes the material U.S. federal income tax consequences of the acquisition, ownership and disposition of our common stock acquired in this offering by Non-U.S. Holders (as defined below). This discussion does not address all aspects of U.S. federal income taxes, does not discuss the potential application of the alternative minimum tax or Medicare Contribution tax and does not deal with state or local taxes, U.S. federal gift and estate tax laws, except to the limited extent provided below, or any non-U.S. tax consequences that may be relevant to Non-U.S. Holders in light of their particular circumstances.

Special rules different from those described below may apply to certain Non-U.S. Holders that are subject to special treatment under the Internal Revenue Code of 1986, as amended, or Code, such as:

- insurance companies, banks and other financial institutions;
- tax-exempt organizations (including private foundations) and tax-qualified retirement plans;
- foreign governments and international organizations;
- broker-dealers and traders in securities;
- U.S. expatriates and certain former citizens or long-term residents of the United States;
- persons that own, or are deemed to own, more than 5% of our capital stock;
- "controlled foreign corporations," "passive foreign investment companies" and corporations that accumulate earnings to avoid U.S. federal income tax;
- persons that hold our common stock as part of a "straddle," "hedge," "conversion transaction," "synthetic security" or integrated investment or other risk reduction strategy;
- persons who do not hold our common stock as a capital asset within the meaning of Section 1221 of the Code (generally, for investment purposes); and
- partnerships and other pass-through entities, and investors in such pass-through entities (regardless of their places of organization or formation).

Such Non-U.S. Holders are urged to consult their own tax advisors to determine the U.S. federal, state, local and other tax consequences that may be relevant to them.

Furthermore, the discussion below is based upon the provisions of the Code, and Treasury regulations, rulings and judicial decisions thereunder as of the date hereof, and such authorities may be repealed, revoked or modified, possibly retroactively, and are subject to differing interpretations which could result in U.S. federal income tax consequences different from those discussed below. We have not requested a ruling from the Internal Revenue Service, or IRS, with respect to the statements made and the conclusions reached in the following summary, and there can be no assurance that the IRS will agree with such statements and conclusions or will not take a contrary position regarding the tax consequences described herein, or that any such contrary position would not be sustained by a court.

PERSONS CONSIDERING THE PURCHASE OF OUR COMMON STOCK PURSUANT TO THIS OFFERING SHOULD CONSULT THEIR OWN TAX ADVISORS CONCERNING THE U.S. FEDERAL INCOME TAX CONSEQUENCES OF ACQUIRING, OWNING AND DISPOSING OF OUR COMMON STOCK IN LIGHT OF THEIR PARTICULAR SITUATIONS AS WELL AS ANY CONSEQUENCES ARISING UNDER THE LAWS OF ANY OTHER TAXING JURISDICTION, INCLUDING ANY STATE, LOCAL OR NON-U.S. TAX CONSEQUENCES OR ANY U.S. FEDERAL NON-INCOME TAX CONSEQUENCES, AND THE POSSIBLE APPLICATION OF TAX TREATIES.

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For the purposes of this discussion, a "Non-U.S. Holder" is, for U.S. federal income tax purposes, a beneficial owner of common stock that is not a U.S. Holder or a partnership for U.S. Federal income tax purposes. A "U.S. Holder" means a beneficial owner of our common stock that is for U.S. federal income tax purposes (a) an individual citizen or resident of the United States, (b) a corporation or other entity taxable as a corporation for U.S. federal income tax purposes, created or organized in or under the laws of the United States, any state thereof or the District of Columbia, (c) an estate the income of which is subject to U.S. federal income taxation regardless of its source, or (d) a trust if it (1) is subject to the primary supervision of a court within the United States and one or more U.S. persons (within the meaning of Section 7701(a)(30) of the Code) have the authority to control all substantial decisions of the trust or (2) has a valid election in effect under applicable U.S. Treasury regulations to be treated as a U.S. person.

If you are an individual non-U.S. citizen, you may, in some cases, be deemed to be a resident alien (as opposed to a nonresident alien) by virtue of being present in the United States for at least 31 days in the calendar year and for an aggregate of at least 183 days during a three-year period ending in the current calendar year. Generally, for this purpose, all the days present in the current year, one-third of the days present in the immediately preceding year, and one-sixth of the days present in the second preceding year, are counted.

Resident aliens are generally subject to U.S. federal income tax as if they were U.S. citizens. Individuals who are uncertain of their status as resident or nonresident aliens for U.S. federal income tax purposes are urged to consult their own tax advisors regarding the U.S. federal income tax consequences of the ownership or disposition of our common stock.

Distributions

We do not expect to make any distributions on our common stock in the foreseeable future. If we do make distributions on our common stock, however, such distributions made to a Non-U.S. Holder of our common stock will constitute dividends for U.S. tax purposes to the extent paid out of our current or accumulated earnings and profits (as determined under U.S. federal income tax principles). Distributions in excess of our current and accumulated earnings and profits will constitute a return of capital that is applied against and reduces, but not below zero, a Non-U.S. Holder's adjusted tax basis in our common stock. Any remaining excess will be treated as gain realized on the sale or exchange of our common stock as described below under the section titled "—Gain on Disposition of Our Common Stock."

Any distribution on our common stock that is treated as a dividend paid to a Non-U.S. Holder that is not effectively connected with the holder's conduct of a trade or business in the United States will generally be subject to withholding tax at a 30% rate or such lower rate as may be specified by an applicable income tax treaty between the United States and the Non-U.S. Holder's country of residence. To obtain a reduced rate of withholding under a treaty, a Non-U.S. Holder generally will be required to provide us with a properly executed IRS Form W-8BEN, IRS Form W-8BEN-E or other appropriate form, certifying the Non-U.S. Holder's entitlement to benefits under that treaty. Such form must be provided prior to the payment of dividends and must be updated periodically. If a Non-U.S. Holder holds stock through a financial institution or other agent acting on the holder's behalf, the holder will be required to provide appropriate documentation to such agent. The holder's agent may then be required to provide certification to us or our paying agent, either directly or through other intermediaries. If you are eligible for a reduced rate of U.S. withholding tax under an income tax treaty, you should consult with your own tax advisor to determine if you are able to obtain a refund or credit of any excess amounts withheld by timely filing an appropriate claim for a refund with the IRS.

We generally are not required to withhold tax on dividends paid to a Non-U.S. Holder that are effectively connected with the holder's conduct of a trade or business within the United States (and, if

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required by an applicable income tax treaty, are attributable to a permanent establishment that the holder maintains in the United States) if a properly executed IRS Form W-8ECI, stating that the dividends are so connected, is furnished to us (or, if stock is held through a financial institution or other agent, to the agent). In general, such effectively connected dividends will be subject to U.S. federal income tax on a net income basis at the regular graduated rates applicable to U.S. persons, unless a specific treaty exemption applies. A corporate Non-U.S. Holder receiving effectively connected dividends may also be subject to an additional "branch profits tax," which is imposed, under certain circumstances, at a rate of 30% (or such lower rate as may be specified by an applicable treaty) on the corporate Non-U.S. Holder's effectively connected earnings and profits, subject to certain adjustments.

See also the section below titled "—Foreign Accounts" for additional withholding rules that may apply to dividends paid to certain foreign financial institutions or non-financial foreign entities.

Gain on Disposition of Our Common Stock

Subject to the discussion below under the sections titled "—Backup Withholding and Information Reporting" and "—Foreign Accounts," a Non-U.S. Holder generally will not be subject to U.S. federal income tax with respect to gain realized on a sale or other disposition of our common stock unless (a) the gain is effectively connected with a trade or business of the holder in the United States (and, if required by an applicable income tax treaty, is attributable to a permanent establishment that the holder maintains in the United States), (b) the Non-U.S. Holder is a nonresident alien individual and is present in the United States for 183 or more days in the taxable year of the disposition and certain other conditions are met, or (c) we are or have been a "United States real property holding corporation" within the meaning of Code Section 897(c)(2) at any time within the shorter of the five-year period preceding such disposition or the holder's holding period in the common stock.

If you are a Non-U.S. Holder described in (a) above, you will be required to pay tax on the net gain derived from the sale at the regular graduated U.S. federal income tax rates applicable to U.S. persons, unless a specific treaty exemption applies. Corporate Non-U.S. Holders described in (a) above may also be subject to the additional branch profits tax at a 30% rate or such lower rate as may be specified by an applicable income tax treaty. If you are an individual Non-U.S. Holder described in (b) above, you will be required to pay a flat 30% tax on the gain derived from the sale, which gain may be offset by U.S. source capital losses (even though you are not considered a resident of the United States), provided you have timely filed U.S. federal income tax returns with respect to such losses. With respect to (c) above, in general, we would be a U.S. real property holding corporation if interests in U.S. real estate comprised (by fair market value) at least half of our assets. We believe that we are not, and do not anticipate becoming, a U.S. real property holding corporation. However, there can be no assurance that we will not become a U.S. real property holding corporation in the future. Even if we are treated as a U.S. real property holding corporation, gain realized by a Non-U.S. Holder on a disposition of our common stock will not be subject to U.S. federal income tax so long as (1) the Non-U.S. Holder owned, directly, indirectly or constructively, no more than five percent of our common stock at all times within the shorter of (i) the five-year period preceding the disposition or (ii) the holder's holding period and (2) our common stock is regularly traded on an established securities market. There can be no assurance that our common stock will continue to qualify as regularly traded on an established securities market.

See the section titled "—Foreign Accounts" for additional information regarding withholding rules that may apply to proceeds of a disposition of our common stock paid to foreign financial institutions or non-financial foreign entities.

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U.S. Federal Estate Tax

The estates of nonresident alien individuals generally are subject to U.S. federal estate tax on property with a U.S. situs. Because we are a U.S. corporation, our common stock will be U.S. situs property and, therefore, will be included in the taxable estate of a nonresident alien decedent, unless an applicable estate tax treaty between the United States and the decedent's country of residence provides otherwise. The terms "resident" and "nonresident" are defined differently for U.S. federal estate tax purposes than for U.S. federal income tax purposes. Investors are urged to consult their own tax advisors regarding the U.S. federal estate tax consequences of the ownership or disposition of our common stock.

Backup Withholding and Information Reporting

Generally, we or certain financial middlemen must report information to the IRS with respect to any dividends we pay on our common stock including the amount of any such dividends, the name and address of the recipient, and the amount, if any, of tax withheld. A similar report is sent to the holder to whom any such dividends are paid. Pursuant to tax treaties or certain other agreements, the IRS may make its reports available to tax authorities in the recipient's country of residence.

Dividends paid by us (or our paying agents) to a Non-U.S. Holder may also be subject to U.S. backup withholding. U.S. backup withholding generally will not apply to a Non-U.S. Holder who provides a properly executed IRS Form W-8BEN or IRS Form W-8BEN-E, as applicable, or otherwise establishes an exemption, provided that the applicable withholding agent does not have actual knowledge or reason to know the holder is a U.S. person.

Under current U.S. federal income tax law, U.S. information reporting and backup withholding requirements generally will apply to the proceeds of a disposition of our common stock effected by or through a U.S. office of any broker, U.S. or non-U.S., unless the Non-U.S. Holder provides a properly executed IRS Form W-8BEN or IRS Form W-8BEN-E, as applicable, or otherwise meets documentary evidence requirements for establishing Non-U.S. Holder status or otherwise establishes an exemption. Generally, U.S. information reporting and backup withholding requirements will not apply to a payment of disposition proceeds to a Non-U.S. Holder where the transaction is effected outside the United States through a non-U.S. office of a non-U.S. broker. Information reporting and backup withholding requirements may, however, apply to a payment of disposition proceeds if the broker has actual knowledge, or reason to know, that the holder is, in fact, a U.S. person. For information reporting purposes, certain brokers with substantial U.S. ownership or operations will generally be treated in a manner similar to U.S. brokers.

Backup withholding is not an additional tax. If backup withholding is applied to you, you should consult with your own tax advisor to determine whether you have overpaid your U.S. federal income tax, and whether you are able to obtain a tax refund or credit of the overpaid amount.

Foreign Accounts

In addition to, and separately from the withholding rules described above, U.S. federal withholding taxes may apply under the Foreign Account Tax Compliance Act, or FATCA, on certain types of payments, including dividends and, on or after January 1, 2019 the gross proceeds of a disposition of our common stock, made to non-U.S. financial institutions and certain other non-U.S. entities. Specifically, a 30% withholding tax may be imposed on dividends on, or, on or after January 1, 2019 gross proceeds from the sale or other disposition of, our common stock paid to a "foreign financial institution" or a "non-financial foreign entity" (each as defined in the Code), unless (1) the foreign financial institution agrees to undertake certain diligence and reporting obligations, (2) the non-financial foreign entity either certifies it does not have any "substantial United States owners" (as defined in the Code) or furnishes identifying information regarding each substantial United States

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owner, or (3) the foreign financial institution or non-financial foreign entity otherwise qualifies for an exemption from these rules. The 30% federal withholding tax described in this paragraph cannot be reduced under an income tax treaty with the United States. If the payee is a foreign financial institution and is subject to the diligence and reporting requirements in (1) above, it must enter into an agreement with the U.S. Department of the Treasury requiring, among other things, that it undertake to identify accounts held by certain "specified United States persons" or "United States-owned foreign entities" (each as defined in the Code), annually report certain information about such accounts, and withhold 30% on certain payments to non-compliant foreign financial institutions and certain other account holders. Foreign financial institutions located in jurisdictions that have an intergovernmental agreement with the United States governing FATCA may be subject to different rules.

Prospective investors should consult their tax advisors regarding the potential application of withholding under FATCA to their investment in our common stock.

EACH PROSPECTIVE INVESTOR SHOULD CONSULT ITS OWN TAX ADVISOR REGARDING THE TAX CONSEQUENCES OF PURCHASING, HOLDING AND DISPOSING OF OUR COMMON STOCK, INCLUDING THE CONSEQUENCES OF ANY PROPOSED CHANGE IN APPLICABLE LAW, AS WELL AS TAX CONSEQUENCES ARISING UNDER ANY STATE, LOCAL, NON-U.S. OR U.S. FEDERAL NON-INCOME TAX LAWS SUCH AS ESTATE AND GIFT TAX.

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UNDERWRITING

Morgan Stanley & Co. LLC, Citigroup Global Markets Inc. and Cowen and Company, LLC are acting as joint book-running managers of the offering and as representatives of the underwriters named below. Subject to the terms and conditions stated in the underwriting agreement dated the date of this prospectus supplement, each underwriter named below has severally agreed to purchase, and we have agreed to sell to that underwriter, the number of shares set forth opposite the underwriter's name.

Underwriter	Number of Shares
Morgan Stanley & Co. LLC	1,451,250
Citigroup Global Markets Inc.	1,044,900
Cowen and Company, LLC	890,100
Stifel, Nicolaus & Company, Incorporated	483,750
Total	3,870,000

The underwriting agreement provides that the obligations of the underwriters to purchase the shares included in this offering are subject to approval of legal matters by counsel and to other conditions. The underwriters are obligated to purchase all the shares (other than those covered by the option to purchase additional shares described below) if they purchase any of the shares.

Shares sold by the underwriters to the public will initially be offered at the initial public offering price set forth on the cover of this prospectus supplement. If all the shares are not sold at the initial offering price, the underwriters may change the offering price and the other selling terms.

If the underwriters sell more shares than the total number set forth in the table above, we have granted to the underwriters an option, exercisable for 30 days from the date of this prospectus supplement, to purchase up to 580,500 additional shares at the public offering price less the underwriting discount. To the extent the option is exercised, each underwriter must purchase a number of additional shares approximately proportionate to that underwriter's initial purchase commitment. Any shares issued or sold under the option will be issued and sold on the same terms and conditions as the other shares that are the subject of this offering.

We, our officers and directors and certain of our stockholders have agreed that, subject to certain exceptions described below, for a period of 90 days from the date of this prospectus supplement, we and they will not, without the prior written consent of Morgan Stanley & Co. LLC, Citigroup Global Markets Inc. and Cowen and Company, LLC, (i) offer, sell, contract to sell, pledge or otherwise dispose of, (or enter into any transaction which is designed to, or might reasonably be expected to, result in the disposition (whether by actual disposition or effective economic disposition due to cash settlement or otherwise) or (ii) enter into any swap or any other agreement or any transaction that transfers, in whole or in part, directly or indirectly, the economic consequence of ownership of, any common stock or any securities convertible into or exercisable or exchangeable for any common stock. Morgan Stanley & Co. LLC, Citigroup Global Markets Inc. and Cowen and Company, LLC in their sole discretion may release any of the securities subject to these lock-up agreements at any time without notice.

This lock-up provision applies to common stock and to securities convertible into or exchangeable or exercisable for common stock. It also applies to common stock owned now or acquired later by the person executing the agreement or for which the person executing the agreement later acquires the power of disposition. The exceptions permit parties to the "lock-up" agreements, among other things and subject to restrictions, to: (a) make certain gifts; (b) make transfers by will or intestate succession; (c) if the party is a corporation, partnership, limited liability company or other business entity, make transfers to any stockholders, partners, members of, or owners of similar equity interests in the party, if

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such transfer is not for value; (d) if the party is a corporation, partnership, limited liability company or other business entity, make transfers (1) in connection with the sale or transfer of all of the party's capital stock, partnership interests, membership interests or other similar equity interests, as the case may be, or all or substantially all of the party's assets, in any such case not undertaken for the purpose of avoiding the restrictions imposed by the "lock-up" agreement or (2) to another corporation, partnership, limited liability company or other business entity so long as the transferee is an affiliate of the party executing the agreement and such transfer is not for value; (e) if the party is a trust, make transfers to the beneficiary of such trust if such transfer is not for value; (f) enter into transactions relating to shares of common stock or other securities convertible into or exchangeable for common stock acquired in open market transactions after completion of the offering, provided that no filing under Section 16(a) of the Exchange Act shall be required or shall be voluntarily made in connection with such transactions; (g) make transfers to us pursuant to agreements under which we have the option to repurchase such common stock or a right of first refusal with respect to transfers of such shares upon termination of service of such party; (h) enter into a 10b5-1 trading plan, provided that such plan does not permit the sale of any common stock during the 90-day lock-up period and no public announcement or filing is made regarding such plan during the 90-day lock-up period; (i) make transfers to us to satisfy tax withholding obligations pursuant to our equity incentive plans; (j) make sales of up to an aggregate of 30,000 shares of common stock pursuant to existing 10b5-1 plans; and (k) make transfers pursuant to a bona-fide third-party tender offer, merger, consolidation or other similar transaction made to all holders of our securities involving a change of control of us, provided that in the event such tender offer, merger, consolidation or other transaction is not completed, such securities held by a party will remain subject to the lock-up agreement; provided that (i) in the case of clauses (a) through (e) above, the transferee agrees to be bound in writing by the lock-up restrictions and (ii) in the case of clauses (c), (d), and (e) above, no filing under Section 16(a) of the Exchange Act shall be required or voluntarily made during the 90-day lock-up period.

The shares are listed on the Nasdaq Global Market under the symbol "LOXO."

The following table shows the underwriting discounts and commissions that we are to pay to the underwriters in connection with this offering. These amounts are shown assuming both no exercise and full exercise of the underwriters' option to purchase additional shares.

	Paid by Loxo	
	No Exercise	Full Exercise
Per share	$ 1.86	$ 1.86
Total	$ 7,198,200	$ 8,277,930

We estimate that our portion of the total expenses of this offering will be $400,000.

We have agreed to reimburse the underwriters up to $30,000 for costs related to clearance of this offering with the Financial Industry Regulatory Authority, Inc.

In connection with the offering, the underwriters may purchase and sell shares in the open market. Purchases and sales in the open market may include short sales, purchases to cover short positions, which may include purchases pursuant to the option to purchase additional shares, and stabilizing purchases.

- Short sales involve secondary market sales by the underwriters of a greater number of shares than they are required to purchase in the offering.

- "Covered" short sales are sales of shares in an amount up to the number of shares represented by the underwriters' option to purchase additional shares.

- "Naked" short sales are sales of shares in an amount in excess of the number of shares represented by the underwriters' option to purchase additional shares.

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- Covering transactions involve purchases of shares either pursuant to the underwriters' option to purchase additional shares or in the open market in order to cover short positions. To close a naked short position, the underwriters must purchase 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 in the open market after pricing that could adversely affect investors who purchase in the offering.

- To close a covered short position, the underwriters must purchase shares in the open market or must exercise the option to purchase additional shares. In determining the source of shares to close 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.

- Stabilizing transactions involve bids to purchase shares so long as the stabilizing bids do not exceed a specified maximum.

Purchases to cover short positions and stabilizing purchases, as well as other purchases by the underwriters for their own accounts, may have the effect of preventing or retarding a decline in the market price of the shares. They may also cause the price of the shares to be higher than the price that would otherwise exist in the open market in the absence of these transactions. The underwriters may conduct these transactions on the Nasdaq Global Market, in the over-the-counter market or otherwise. If the underwriters commence any of these transactions, they may discontinue them at any time.

In addition, in connection with this offering, some of the underwriters (and selling group members) may engage in passive market making transactions in the shares on the Nasdaq Global Market, prior to the pricing and completion of the offering. Passive market making consists of displaying bids on the Nasdaq Global Market no higher than the bid prices of independent market makers and making purchases at prices no higher than those independent bids and effected in response to order flow. Net purchases by a passive market maker on each day are limited to a specified percentage of the passive market maker's average daily trading volume in the shares during a specified period and must be discontinued when that limit is reached. Passive market making may cause the price of the shares to be higher than the price that otherwise would exist in the open market in the absence of those transactions. If the underwriters commence passive market making transactions, they may discontinue them at any time.

Conflicts of Interest

The underwriters are full service financial institutions engaged in various activities, which may include securities trading, commercial and investment banking, financial advisory, investment management, principal investment, hedging, financing and brokerage activities. The underwriters and their respective affiliates have in the past performed commercial banking, investment banking and advisory services for us from time to time for which they have received customary fees and reimbursement of expenses and may, from time to time, engage in transactions with and perform services for us in the ordinary course of their business for which they may receive customary fees and reimbursement of expenses. In the ordinary course of their various business activities, the underwriters and their respective affiliates may make or hold a broad array of investments and actively trade debt and equity securities (or related derivative securities) and financial instruments (which may include bank loans and/or credit default swaps) for their own account and for the accounts of their customers and may at any time hold long and short positions in such securities and instruments. Such investments and securities activities may involve securities and/or instruments of ours or our affiliates. The underwriters and their affiliates may also make investment recommendations and/or publish or express independent research views in respect of such securities or financial instruments and may hold, or recommend to clients that they acquire, long and/or short positions in such securities and instruments.

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We have agreed to indemnify the underwriters against certain liabilities, including liabilities under the Securities Act, or to contribute to payments the underwriters may be required to make because of any of those liabilities.

Notice to Prospective Investors in the European Economic Area

In relation to each member state of the European Economic Area that has implemented the Prospectus Directive (each, a relevant member state), with effect from and including the date on which the Prospectus Directive is implemented in that relevant member state (the relevant implementation date), an offer of shares described in this prospectus supplement may not be made to the public in that relevant member state other than:

- to any legal entity which is a qualified investor as defined in the Prospectus Directive;
- to fewer than 100 or, if the relevant member state has implemented the relevant provision of the 2010 PD Amending Directive, 150 natural or legal persons (other than qualified investors as defined in the Prospectus Directive), as permitted under the Prospectus Directive, subject to obtaining the prior consent of the relevant Dealer or Dealers nominated by us for any such offer; or
- in any other circumstances falling within Article 3(2) of the Prospectus Directive,

provided that no such offer of shares shall require us or any underwriter to publish a prospectus pursuant to Article 3 of the Prospectus Directive.

For purposes of this provision, the expression an "offer of securities to the public" in any relevant member state means the communication in any form and by any means of sufficient information on the terms of the offer and the shares to be offered so as to enable an investor to decide to purchase or subscribe for the shares, as the expression may be varied in that member state by any measure implementing the Prospectus Directive in that member state, and the expression "Prospectus Directive" means Directive 2003/71/EC (and amendments thereto, including the 2010 PD Amending Directive, to the extent implemented in the relevant member state) and includes any relevant implementing measure in the relevant member state. The expression 2010 PD Amending Directive means Directive 2010/73/EU.

The sellers of the shares have not authorized and do not authorize the making of any offer of shares through any financial intermediary on their behalf, other than offers made by the underwriters with a view to the final placement of the shares as contemplated in this prospectus supplement. Accordingly, no purchaser of the shares, other than the underwriters, is authorized to make any further offer of the shares on behalf of the sellers or the underwriters.

Notice to Prospective Investors in the United Kingdom

This prospectus supplement and the accompanying prospectus are 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 (the "Order") or (ii) high net worth entities, and other persons to whom it may lawfully be communicated, falling within Article 49(2)(a) to (d) of the Order (each such person being referred to as a "relevant person"). This prospectus supplement 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.

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Notice to Prospective Investors in France

Neither this prospectus supplement nor any other offering material relating to the shares described in this prospectus supplement has been submitted to the clearance procedures of the *Autorité des Marchés Financiers* or of the competent authority of another member state of the European Economic Area and notified to the *Autorité des Marchés Financiers*. The shares have not been offered or sold and will not be offered or sold, directly or indirectly, to the public in France. Neither this prospectus supplement nor any other offering material relating to the shares has been or will be:

- released, issued, distributed or caused to be released, issued or distributed to the public in France; or
- used in connection with any offer for subscription or sale of the shares to the public in France.

Such offers, sales and distributions will be made in France only:

- to qualified investors (*investisseurs qualifiés*) and/or to a restricted circle of investors (*cercle restreint d'investisseurs*), in each case investing for their own account, all as defined in, and in accordance with articles L.411-2, D.411-1, D.411-2, D.734-1, D.744-1, D.754-1 and D.764-1 of the French *Code monétaire et financier*;
- to investment services providers authorized to engage in portfolio management on behalf of third parties; or
- in a transaction that, in accordance with article L.411-2-II-1°-or-2°-or 3° of the French *Code monétaire et financier* and article 211-2 of the General Regulations (*Règlement Général*) of the *Autorité des Marchés Financiers*, does not constitute a public offer (*appel public à l'épargne*).

The shares may be resold directly or indirectly, only in compliance with articles L.411-1, L.411-2, L.412-1 and L.621-8 through L.621-8-3 of the French *Code monétaire et financier*.

Notice to Prospective Investors in Hong Kong

The shares may not be offered or sold in Hong Kong by means of any document other than (i) in circumstances which do not constitute an offer to the public within the meaning of the Companies Ordinance (Cap. 32, Laws of Hong Kong), or (ii) to "professional investors" within the meaning of the Securities and Futures Ordinance (Cap. 571, Laws of Hong Kong) and any rules made thereunder, or (iii) in other circumstances which do not result in the document being a "prospectus" within the meaning of the Companies Ordinance (Cap. 32, Laws of Hong Kong) and no advertisement, invitation or document relating to the shares 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 in Hong Kong (except if permitted to do so under the laws of Hong Kong) other than with respect to shares which are or are intended to be disposed of only to persons outside Hong Kong or only to "professional investors" within the meaning of the Securities and Futures Ordinance (Cap. 571, Laws of Hong Kong) and any rules made thereunder.

Notice to Prospective Investors in Japan

The shares offered in this prospectus supplement have not been and will not be registered under the Financial Instruments and Exchange Law of Japan. The shares have not been offered or sold and will not be offered or sold, directly or indirectly, in Japan or to or for the account of any resident of Japan (including any corporation or other entity organized under the laws of Japan), except (i) pursuant to an exemption from the registration requirements of the Financial Instruments and Exchange Law and (ii) in compliance with any other applicable requirements of Japanese law.

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Notice to Prospective Investors in Singapore

This prospectus supplement has not been registered as a prospectus with the Monetary Authority of Singapore. Accordingly, this prospectus supplement and any other document or material in connection with the offer or sale, or invitation for subscription or purchase, of the shares may not be circulated or distributed, nor may the shares be offered or sold, or be made the subject of an invitation for subscription or purchase, whether directly or indirectly, to persons in 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, in each case subject to compliance with conditions set forth in the SFA.

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

- 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

- 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,

shares, debentures and units of shares and debentures of that corporation or the beneficiaries' rights and interest (howsoever described) in that trust shall not be transferred within six months after that corporation or that trust has acquired the shares pursuant to an offer made under Section 275 of the SFA except:

- to an institutional investor (for corporations, under Section 274 of the SFA) or to a relevant person defined in Section 275(2) of the SFA, or to any person pursuant to an offer that is made on terms that such shares, debentures and units of shares and debentures of that corporation or such rights and interest in that trust are acquired at a consideration of not less than S$200,000 (or its equivalent in a foreign currency) for each transaction, whether such amount is to be paid for in cash or by exchange of securities or other assets, and further for corporations, in accordance with the conditions specified in Section 275 of the SFA;

- where no consideration is or will be given for the transfer; or

- where the transfer is by operation of law.

Notice to Prospective Investors in Canada

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

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

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

Notice to Prospective Investors in Australia

No prospectus or other disclosure document (as defined in the Corporations Act 2001 (Cth) of Australia ("Corporations Act")) in relation to the common stock has been or will be lodged with the Australian Securities & Investments Commission ("ASIC"). This document has not been lodged with ASIC and is only directed to certain categories of exempt persons. Accordingly, if you receive this document in Australia:

(a) you confirm and warrant that you are either:

(i) a "sophisticated investor" under section 708(8)(a) or (b) of the Corporations Act;

(ii) a "sophisticated investor" under section 708(8)(c) or (d) of the Corporations Act and that you have provided an accountant's certificate to us 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;

(iii) a person associated with the company under section 708(12) of the Corporations Act; or

(iv) a "professional investor" within the meaning of section 708(11)(a) or (b) of the Corporations Act, and 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 document is void and incapable of acceptance; and

(b) you warrant and agree that you will not offer any of the common stock for resale in Australia within 12 months of that common stock being issued unless any such resale offer is exempt from the requirement to issue a disclosure document under section 708 of the Corporations Act.

Notice to Prospective Investors in Switzerland

This document as well as any other material relating to the shares of our common stock that are the subject of the offering contemplated by this prospectus do not constitute an issue prospectus pursuant to Article 652a or Article 1156 of the Swiss Code of Obligations. Our common stock will not be listed on the SWX Swiss Exchange and, therefore, the documents relating to our common stock, including, but not limited to, this document, do not claim to comply with the disclosure standards of the listing rules of SWX Swiss Exchange and corresponding prospectus schemes annexed to the listing rules of the SWX Swiss Exchange. Our common stock is being offered in Switzerland by way of a private placement, i.e. to a small number of selected investors only, without any public offer and only to investors who do not purchase shares of our common stock with the intention to distribute them to the public. The investors will be individually approached by us from time to time. This document as well as any other material relating to our common stock is personal and confidential and does not constitute an offer to any other person. This document may only be used by those investors to whom it has been handed out in connection with the offering described herein and may neither directly nor indirectly be distributed or made available to other persons without our express consent. It may not be used in connection with any other offer and shall in particular not be copied and/or distributed to the public in (or from) Switzerland.

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Notice to Prospective Investors in Chile

The shares are not registered in the Securities Registry (Registro de Valores) or subject to the control of the Chilean Securities and Exchange Commission (Superintendencia de Valores y Seguros de Chile). This prospectus supplement and other offering materials relating to the offer of the shares do not constitute a public offer of, or an invitation to subscribe for or purchase, the shares in the Republic of Chile, other than to individually identified purchasers pursuant to a private offering within the meaning of Article 4 of the Chilean Securities Market Act (Ley de Mercado de Valores) (an offer that is not "addressed to the public at large or to a certain sector or specific group of the public").

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LEGAL MATTERS

The validity of the shares of common stock offered hereby will be passed upon for us by Fenwick & West LLP, San Francisco, California. Davis Polk & Wardwell LLP, Menlo Park, California is acting as counsel to the underwriters.

EXPERTS

The financial statements incorporated by reference in this prospectus supplement from our Annual Report on Form 10-K for the year ended December 31, 2015 have been audited by CohnReznick LLP, independent registered public accounting firm, as stated in its report, which is incorporated herein by reference. Such financial statements have been so incorporated in reliance upon the report of such firm given upon its authority as experts in accounting and auditing.

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WHERE YOU CAN FIND MORE INFORMATION

We are subject to the informational requirements of the Securities Exchange Act of 1934, as amended, and are required to file annual, quarterly and other reports, proxy statements and other information with the SEC. You may request copies of these reports, proxy statements and other information without charge, by written or telephonic request directed to Loxo Oncology, Inc., Attn: Investor Relations, 281 Tresser Boulevard, 9th Floor, Stamford, CT, 06901, telephone number (203) 653-3880. You may also inspect and copy these reports, proxy statements and other information at the public reference facilities maintained by the SEC in Washington, D.C., 100 F Street N.E., Washington, D.C. 20549. Copies of such materials can be obtained from the SEC's public reference section at prescribed rates. You may obtain information on the operation of the public reference rooms by calling the SEC at (800) SEC-0330. Additionally, the SEC maintains an Internet site (http://www.sec.gov) that contains reports, proxy and information statements, and various other information about us. You may also inspect the documents described herein at our principal executive offices, 281 Tresser Boulevard, 9th Floor, Stamford, CT, 06901, during normal business hours.

Information about us is also available at our website at http://www.loxooncology.com. However, the information on, or that can be accessed through, our website is not a part of this prospectus supplement or the accompanying prospectus and is not incorporated by reference into this prospectus supplement (other than those filings with the SEC that we specifically incorporate by reference into this prospectus supplement or accompanying prospectus).

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

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INCORPORATION OF INFORMATION BY REFERENCE

The SEC allows us to "incorporate by reference" information that we file with the SEC, which means that we can disclose important information to you by referring you to those other documents. The information incorporated by reference is an important part of this prospectus supplement and the accompanying prospectus, and information we file later with the SEC will automatically update and supersede this information. We incorporate by reference the documents listed below and any future filings we make with the SEC under Section 13(a), 13(c), 14, or 15(d) of the Exchange Act prior to the termination of any offering of securities made by this prospectus:

- our Annual Report on Form 10-K for the fiscal year ended December 31, 2015 filed with the SEC on March 15, 2016, including certain information incorporated by reference therein from our Definitive Proxy Statement for our 2016 annual meeting of stockholders filed with the SEC on April 18, 2016;
- our Quarterly Reports on Form 10-Q for the quarters ended March 31, 2016, June 30, 2016 and September 30, 2016 filed with the SEC on May 4, 2016, August 3, 2016 and November 2, 2016, respectively;
- our Current Reports on Form 8-K filed on January 7, 2016, May 12, 2016, June 13, 2016, and November 9, 2016; and
- the description of our common stock contained in our registration statement on Form 8-A filed with the SEC on July 22, 2014 under Section 12 of the Exchange Act, including any amendment or report filed for the purpose of updating such description.

Upon written or oral request, we will provide without charge to each person, including any beneficial owner, to whom this prospectus supplement and the accompanying prospectus are delivered, a copy of any or all of such information that has been incorporated herein by reference (other than exhibits to such documents unless such exhibits are specifically incorporated by reference into the documents that this prospectus supplement and accompany prospectus incorporates). Written or oral requests for copies should be directed Loxo Oncology, Inc., Attn: Investor Relations, 281 Tresser Boulevard, 9th Floor, Stamford, CT, 06901, telephone number (203) 653-3880. See the section of this prospectus entitled "Where You Can Find More Information" for information concerning how to read and obtain copies of materials that we file with the SEC at the SEC's public offices.

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PROSPECTUS

$250,000,000

Loxo Oncology, Inc.

Common Stock, Preferred Stock, Debt Securities, Warrants, Subscription Rights and Units

From time to time, we or selling security holders may offer up to $250,000,000 aggregate dollar amount of shares of our common stock or preferred stock, debt securities, warrants to purchase our common stock, preferred stock or debt securities, subscription rights to purchase our common stock, preferred stock or debt securities and/or units consisting of some or all of these securities, in any combination, together or separately, in one or more offerings, in amounts, at prices and on the terms that we will determine at the time of the offering and which will be set forth in a prospectus supplement and any related free writing prospectus. The prospectus supplement and any related free writing prospectus may also add, update or change information contained in this prospectus. The total amount of these securities will have an initial aggregate offering price of up to $250,000,000.

You should read this prospectus, the information incorporated, or deemed to be incorporated, by reference in this prospectus, and any applicable prospectus supplement and related free writing prospectus carefully before you invest.

Our common stock is traded on the NASDAQ Global Market under the symbol "LOXO." On November 1, 2016 the last reported sales price for our common stock was $20.49 per share. None of the other securities we may offer are currently traded on any securities exchange. The applicable prospectus supplement and any related free writing prospectus will contain information, where applicable, as to any other listing on the NASDAQ Global Market or any securities market or exchange of the securities covered by the prospectus supplement and any related free writing prospectus.

An investment in our securities involves a high degree of risk. You should carefully consider the information under the heading "Risk Factors" beginning on page 5 of this prospectus before investing in our securities.

Common stock, preferred stock, debt securities, warrants, subscription rights and/or units may be sold by us or selling security holders 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 entitled "Plan of Distribution" in this prospectus. If any underwriters, dealers or agents are involved in the sale of any securities with respect to which this prospectus is being delivered, the names of such underwriters or agents and any applicable fees, discounts or commissions, details regarding over-allotment options, if any, and the net proceeds to us 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.

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

The date of this prospectus is November 16, 2016

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ABOUT THIS PROSPECTUS

This prospectus is part of a registration statement that we filed with the Securities and Exchange Commission (the SEC) using a "shelf" registration process. Under this shelf registration process, from time to time, we may sell any combination of the securities described in this prospectus in one or more offerings, up to a total dollar amount of $250,000,000. We have provided to you in this prospectus a general description of the securities we may offer. Each time we sell securities under this shelf registration process, we will provide a prospectus supplement that will contain specific information about the terms of the offering. We may also add, update or change in the prospectus supplement any of the information contained in this prospectus. To the extent there is a conflict between the information contained in this prospectus and the prospectus supplement, you should rely on the information in the 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 this prospectus or any prospectus supplement—the statement in the document having the later date modifies or supersedes the earlier statement. You should read both this prospectus and any prospectus supplement together with additional information described under the next heading "Where You Can Find More Information."

You should rely only on the information contained in or incorporated by reference into this prospectus or any applicable prospectus supplement. No dealer, salesperson or any other person is authorized to give any information or to make any representation other than the information and representations contained in or incorporated by reference into this prospectus or any applicable prospectus supplement. If different information is given or different representations are made, you may not rely on that information or those representations as having been authorized by us. You may not imply from the delivery of this prospectus and any applicable prospectus supplement, nor from a sale made under this prospectus and any applicable prospectus supplement, that our affairs are unchanged since the date of this prospectus and any applicable prospectus supplement or that the information contained in any document incorporated by reference is accurate as of any date other than the date of the document incorporated by reference, regardless of the time of delivery of this prospectus and any applicable prospectus supplement or any sale of a security. This prospectus and any applicable prospectus supplement may only be used where it is legal to sell the securities.

THIS PROSPECTUS MAY NOT BE USED TO OFFER AND SELL SECURITIES UNLESS IT IS ACCOMPANIED BY A PROSPECTUS SUPPLEMENT.

In this prospectus, unless the context otherwise requires, the terms "Loxo," the "Company," "we," "us," and "our" refer to Loxo Oncology, Inc., a Delaware corporation.

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PROSPECTUS SUMMARY

This summary may not contain all the information that you should consider before investing in securities. You should read the entire prospectus and the information incorporated by reference in this prospectus carefully, including "Risk Factors" and the financial data and related notes and other information incorporated by reference, before making an investment decision.

Company Overview

Loxo Oncology is a biopharmaceutical company innovating the development of highly selective medicines for patients with genetically defined cancers. Our pipeline focuses on cancers that are uniquely dependent on single gene abnormalities, such that a single drug has the potential to treat the cancer with dramatic effect. We believe that the most selective, purpose-built medicines have the highest probability of maximally inhibiting the intended target, thereby delivering best-in-class disease control and safety. Our management team seeks out experienced industry partners, world-class scientific advisors and innovative clinical-regulatory approaches to deliver new cancer therapies to patients as quickly and efficiently as possible.

With our scientific knowledge, collaborative partnerships and targeted approach, we are developing multiple small molecule therapeutics utilizing focused clinical development strategies in well-defined patient populations. LOXO-101, the only selective TRK inhibitor currently in clinical development, is being evaluated in a global Phase 2 multi-center basket study in patients with solid tumors that harbor TRK gene fusions. LOXO-101 is also being evaluated in an ongoing Phase 1 clinical trial and a Phase 1 trial in pediatric patients. We also have pre-clinical programs in development, through our collaboration with Array, for LOXO-195, RET, FGFR and other targets.

As genetic testing in cancer becomes more routine, we are learning that cancers arising in diverse sites in the body may share the same type of genetic alterations. Increasingly, tumors may be identified and treated according to their distinguishing genetic alterations, while in the past, the organ of origin was most important. Both research and clinical data suggest that some tumors, while having many identifiable genetic alterations, are primarily dependent on a single activated kinase for their proliferation and survival. This dependency, often referred to as oncogene addiction, renders such tumors highly susceptible to small molecule inhibitors targeting the relevant alteration.

We identify and prioritize our targets in two ways. First, we use clinical trial data to assess the response signals of drugs in development and identify those that show promise but also demonstrate drug-specific limitations such as poor absorption, poor distribution or unwanted side effects. Second, we evaluate academic research to uncover novel targets with emerging validation. Once the target is identified, we then employ advanced third-party technology to develop product candidates intended to have enhanced target engagement and specificity. We implement a stepwise approach to clinical development designed to reduce risk and identify response signals early in development. In early-stage trials we plan to evaluate our product candidates in well-defined patient populations and believe that this gives us a higher likelihood of demonstrating a clinical benefit. This approach allows for the possibility of rapid clinical development and expedited regulatory strategies. We intend to develop companion diagnostics when appropriate, with the help of technology partners, to identify patients whose tumors harbor relevant genetic alterations.

We have demonstrated the promise of this model through the rapid advancement of our TRK inhibitor, LOXO-101, into the clinic. The appearance of TRK alterations in multiple cancers, coupled with recent data in lung cancer, head and neck cancer, melanoma, colorectal cancer, sarcoma and breast cancer, suggests TRK may behave as an oncogenic driver. In April 2016, we presented updated data from our Phase 1 trial at the 2016 American Association for Cancer Research (AACR) Annual Meeting in New Orleans, and also in April 2016, we published a case report in the online edition of the peer-reviewed journal Pediatric Blood and Cancer, co-authored with Nemours Children's Hospital,

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Northwestern University and St. Jude Children's Research Hospital, describing a partial response in the first patient with a TRK fusion cancer enrolled in the pediatric Phase 1 dose-escalation trial of LOXO-101. We have exclusive rights to issued composition of matter patents covering LOXO-101 that expire in 2029.

To build a pipeline of targeted therapeutics, we entered into a multi-target collaboration with Array BioPharma Inc., or Array, to leverage its expertise in building highly selective and potent kinase inhibitors. The collaboration was designed around a broad list of targets to give us the flexibility to prioritize the most promising of these targets for advancement into clinical development. We believe that this collaboration will allow us to develop multiple targeted therapeutics in a rapid and capital-efficient manner. We retain worldwide commercial rights for all of our product candidates.

In July 2016, the U.S. Food and Drug Administration (FDA) granted Breakthrough Therapy Designation to LOXO-101 "for the treatment of unresectable or metastatic solid tumors with NTRK-fusion proteins in adult and pediatric patients who require systemic therapy and who have either progressed following prior treatment or who have no acceptable alternative treatments." The LOXO-101 Breakthrough Therapy Designation application, submitted approximately 60 days prior to designation receipt, included data from the ongoing Phase 1 dose-escalation study of LOXO-101 in adult patients with advanced solid tumors, the ongoing Phase 1 pediatric study of LOXO-101 in patients with advanced solid tumors or primary CNS tumors, and the ongoing Phase 2 basket trial of LOXO-101 in adult cancer patients whose tumors harbor TRK fusions.

The Securities We May Offer

With this prospectus, we may offer common stock, preferred stock, debt securities, warrants, subscription rights to purchase our common stock, preferred stock or debt securities, and/or units consisting of some or all of these securities in any combination. The aggregate offering price of securities that we offer with this prospectus will not exceed $250,000,000. Each time we offer securities with this prospectus, we will provide offerees with a prospectus supplement that will contain the specific terms of the securities being offered. The following is a summary of the securities we may offer with this prospectus.

Common Stock

We may offer shares of our common stock, par value $0.0001 per share.

Preferred Stock

We may offer shares of our preferred stock, par value $0.0001 per share, in one or more series. Our board of directors or a committee designated by the board will determine the dividend, voting, conversion and other rights of the series of shares of preferred stock being offered. Each series of preferred stock will be more fully described in the particular prospectus supplement that will accompany this prospectus, including redemption provisions, rights in the event of our liquidation, dissolution or the winding up, voting rights and rights to convert into common stock.

Debt Securities

We may offer general obligations, which may be secured or unsecured, senior or subordinated and convertible into shares of our common stock or preferred stock. In this prospectus, we refer to the senior debt securities and the subordinated debt securities together as the "debt securities." Our board of directors will determine the terms of each series of debt securities being offered.

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We will issue the debt securities under an indenture between us and a trustee. In this document, we have summarized general features of the debt securities from the indenture. We encourage you to read the indenture, which is an exhibit to the registration statement of which this prospectus is a part.

Warrants

We may offer warrants for the purchase of debt securities, shares of preferred stock or shares of common stock. We may issue warrants independently or together with other securities. Our board of directors will determine the terms of the warrants.

Subscription Rights

We may offer subscription rights for the purchase of common stock, preferred stock or debt securities. We may issue subscription rights independently or together with other securities. Our board of directors will determine the terms of the subscription rights.

Units

We may offer units consisting of some or all of the securities described above, in any combination, including common stock, preferred stock, warrants and/or debt securities. The terms of these units will be set forth in a prospectus supplement. The description of the terms of these units in the related prospectus supplement will not be complete. You should refer to the applicable form of unit and unit agreement for complete information with respect to these units.

* * *

We were incorporated in Delaware in 2013 as Loxo Oncology, Inc. Our principal executive offices are located at 281 Tresser Blvd., 9th Floor, Stamford, CT, 06901, and our telephone number is (203) 653-3880. We have research and development operations and corporate offices in Stamford, CT and South San Francisco, CA.

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RATIO OF EARNINGS TO FIXED CHARGES

The following table sets forth our dollar coverage deficiency. The ratio of earnings to fixed charges is not disclosed since it is a negative number in each year and period shown below. Any time we offer debt securities pursuant to this prospectus, we will provide an updated table setting forth our ratio of earnings to fixed charges on a historical basis in the applicable prospectus supplement, if required. Any time we offer shares of preferred stock pursuant to this prospectus, we will provide a table setting forth our ratio of combined fixed charges and preferred stock dividends to earnings, if required.

Period From May 9, 2013 (Date of Inception) to December 31, 2013	Year Ended December 31, 2014	Year Ended December 31, 2015	Nine Months Ended September 30, 2016
(1)	(1)	(1)	(1)

(1) Due to our net losses for the periods presented earnings were insufficient to cover fixed charges. For this reason, no ratios are provided.

RISK FACTORS

An investment in our securities involves a high degree of risk. The prospectus supplement applicable to each offering of securities will contain a discussion of the risks applicable to an investment in our securities. Prior to making a decision about investing in our securities, you should carefully consider the specific factors discussed under the heading "Risk Factors" in the applicable prospectus supplement, together with all of the other information contained or incorporated by reference in the prospectus supplement or appearing or incorporated by reference in this prospectus. You should also consider the risks, uncertainties and assumptions discussed under Part II, Item 1A, "Risk Factors," in our Quarterly Report on Form 10-Q for the quarterly period ended September 30, 2016, which is incorporated herein by reference, and may be amended, supplemented or superseded from time to time by other reports we file with the SEC in the future. The risks and uncertainties we have described are not the only ones we face. Additional risks and uncertainties not presently known to us or that we currently deem immaterial may also affect our operations.

FORWARD-LOOKING STATEMENTS

This prospectus and documents incorporated herein by reference contain "forward-looking statements" within the meaning of the Private Securities Litigation Reform Act of 1995. These forward-looking statements involve a number of risks and uncertainties. We caution readers that any forward-looking statement is not a guarantee of future performance and that actual results could differ materially from those contained in the forward-looking statement. These statements are based on current expectations of future events. Such statements include, but are not limited to, statements about future financial and operating results, plans, objectives, expectations and intentions, costs and expenses, interest rates, outcome of contingencies, financial condition, results of operations, liquidity, cost savings, objectives of management, business strategies, debt financing, clinical trial timing and plans, the achievement of clinical and commercial milestones, the advancement of our technologies and our proprietary and partnered products and product candidates, and other statements that are not historical facts. You can find many of these statements by looking for words like "believes," "expects," "anticipates," "estimates," "may," "might," "should," "will," "could," "plan," "intend," "project," "seek" or similar expressions in this prospectus or in documents incorporated by reference into this prospectus. We intend that such forward-looking statements be subject to the safe harbors created thereby.

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These forward-looking statements are based on the current beliefs and expectations of our management and are subject to significant risks and uncertainties. If underlying assumptions prove inaccurate or unknown risks or uncertainties materialize, actual results may differ materially from current expectations and projections. Factors that might cause such a difference include those discussed in Part II, Item 1A "Risk Factors" in our Quarterly Report on Form 10-Q for the quarter ended September 30, 2016, as well as those discussed in this prospectus and in the documents incorporated by reference into this prospectus. You are cautioned not to place undue reliance on these forward-looking statements, which speak only as of the date of this prospectus or, in the case of documents referred to or incorporated by reference, the date of those documents.

All subsequent written or oral forward-looking statements attributable to us or any person acting on our behalf are expressly qualified in their entirety by the cautionary statements contained or referred to in this section. We do not undertake any obligation to release publicly any revisions to these forward-looking statements to reflect events or circumstances after the date of this prospectus or to reflect the occurrence of unanticipated events, except as may be required under applicable U.S. securities law. If we do update one or more forward-looking statements, no inference should be drawn that we will make additional updates with respect to those or other forward-looking statements.

WHERE YOU CAN FIND MORE INFORMATION

We are subject to the informational requirements of the Securities Exchange Act of 1934, as amended (the Exchange Act) and are required to file annual, quarterly and other reports, proxy statements and other information with the SEC. You may inspect and copy these reports, proxy statements and other information at the public reference facilities maintained by the SEC in Washington, D.C., 100 F Street N.E., Washington, D.C. 20549. Copies of such materials can be obtained from the SEC's public reference section at prescribed rates. You may obtain information on the operation of the public reference rooms by calling the SEC at (800) SEC-0330. Additionally, the SEC maintains an Internet site (http://www.sec.gov) that contains reports, proxy and information statements, and various other information about us. You may also inspect the documents described herein at our principal executive offices, 281 Tresser Blvd., 9th Floor, Stamford, CT 06901, during normal business hours.

Information about us is also available at our website at http://www.loxooncology.com. However, the information on our website is not a part of this prospectus and is not incorporated by reference into this prospectus.

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INCORPORATION OF INFORMATION BY REFERENCE

The SEC allows us to "incorporate by reference" information that we file with the SEC, which means that we can disclose important information to you by referring you to those other documents. The information incorporated by reference is an important part of this prospectus, and information we file later with the SEC will automatically update and supersede this information. We incorporate by reference the documents listed below and any future filings we make with the SEC under Section 13(a), 13(c), 14, or 15(d) of the Exchange Act prior to the termination of any offering of securities made by this prospectus:

- our Annual Report on Form 10-K for the fiscal year ended December 31, 2015 filed with the SEC on March 15, 2016, including certain information incorporated by reference therein from our Definitive Proxy Statement for our 2016 annual meeting of stockholders filed with the SEC on April 18, 2016;
- our Quarterly Reports on Form 10-Q for the quarter ended March 31, 2016, June 30, 2016 and September 30, 2016 and filed with the SEC on May 4, 2016, August 3, 2016 and November 2, 2016, respectively;
- our Current Reports on Form 8-K filed on January 7, 2016, May 12, 2016 and June 13, 2016;
- the description of our common stock contained in our registration statement on Form 8-A filed with the SEC on July 22, 2014 under Section 12 of the Exchange Act, including any amendment or report filed for the purpose of updating such description; and
- filings we make with the SEC pursuant to the Exchange Act after the date of the initial registration statement, of which this prospectus is a part, and prior to the effectiveness of the registration statement.

Upon written or oral request, we will provide without charge to each person, including any beneficial owner, to whom this prospectus is delivered, a copy of any or all of such information that has been incorporated herein by reference (other than exhibits to such documents unless such exhibits are specifically incorporated by reference into the documents that this prospectus incorporates). Written or oral requests for copies should be directed Loxo Oncology, Inc., Attn: Investor Relations, 281 Tresser Blvd., 9th Floor, Stamford, CT 06901, telephone number (203) 653-3880. See the section of this prospectus entitled "Where You Can Find More Information" for information concerning how to read and obtain copies of materials that we file with the SEC at the SEC's public offices.

Any statement contained in this prospectus, or in a document all or a portion of which is incorporated by reference, shall be modified or superseded for purposes of this prospectus to the extent that a statement contained in this prospectus, any prospectus supplement or any document incorporated by reference modifies or supersedes such statement. Any such statement so modified or superseded shall not, except as so modified or superseded, constitute a part of this prospectus.

USE OF PROCEEDS

We will retain broad discretion over the use of the net proceeds to us from the sale of our securities under this prospectus. Unless otherwise provided in the applicable prospectus supplement, we intend to use the net proceeds from the sale of securities under this prospectus for general corporate purposes, which may include funding research and development, increasing our working capital, reducing indebtedness, acquisitions or investments in businesses, products or technologies that are complementary to our own and capital expenditures. We will set forth in the prospectus supplement our intended use for the net proceeds received from the sale of any securities. Pending the application of the net proceeds, we intend to invest the net proceeds in short-term or long-term, investment-grade, interest-bearing securities.

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PLAN OF DISTRIBUTION

We may sell the securities covered by this prospectus to one or more underwriters for public offering and sale by them, and may also sell the securities to investors directly or through agents. We will name any underwriter or agent involved in the offer and sale of securities in the applicable prospectus supplement. We have reserved the right to sell or exchange securities directly to investors on our own behalf in jurisdictions where we are authorized to do so. We may distribute the 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 time of sale;
- at prices related to such prevailing market prices; or
- at negotiated prices.

We may directly solicit offers to purchase the securities being offered by this prospectus. We may also designate agents to solicit offers to purchase the securities from time to time. We will name in a prospectus supplement any agent involved in the offer or sale of our securities. Unless otherwise indicated in a prospectus supplement, an agent will be acting on a best efforts basis, and a dealer will purchase securities as a principal for resale at varying prices to be determined by the dealer.

If we utilize an underwriter in the sale of the securities being offered by this prospectus, we will execute an underwriting agreement with the underwriter at the time of sale and we will provide the name of any underwriter in the prospectus supplement that the underwriter will use to make resales of the securities to the public. In connection with the sale of the securities, we, or the purchasers of securities for whom the underwriter may act as agent, may compensate the underwriter in the form of underwriting discounts or commissions. The underwriter may sell the securities to or through dealers, and those dealers may receive compensation in the form of discounts, concessions or commissions from the underwriters or commissions from the purchasers for whom they may act as agent.

We will provide in the applicable prospectus supplement any compensation we pay to underwriters, dealers, or agents in connection with the offering of the securities, and any discounts, concessions or commissions allowed by underwriters to participating dealers. Underwriters, dealers and agents participating in the distribution of the securities may be deemed to be underwriters within the meaning of the Securities Act of 1933 (the Securities Act), and any discounts and commissions received by them and any profit realized by them on resale of the securities may be deemed to be underwriting discounts and commissions. We may enter into agreements to indemnify underwriters, dealers and agents against civil liabilities, including liabilities under the Securities Act, and to reimburse them for certain expenses. We may grant underwriters who participate in the distribution of our securities under this prospectus an option to purchase additional securities to cover any over-allotments in connection with the distribution.

The securities we offer under this prospectus may or may not be listed through the NASDAQ Global Market or any other securities exchange. To facilitate the offering of securities, certain persons participating in the offering may engage in transactions that stabilize, maintain or otherwise affect the price of the securities. This may include short sales of the securities, which involves the sale by persons participating in the offering of more securities than we sold to them. In these circumstances, these persons would cover such short positions by making purchases in the open market or by exercising their option to purchase additional securities. In addition, these persons may stabilize or maintain the price of the securities by bidding for or purchasing securities in the open market or by imposing penalty bids, whereby selling concessions allowed to dealers participating in the offering may be reclaimed if securities sold by them are repurchased in connection with stabilization transactions. The effect of these

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transactions may be to stabilize or maintain the market price of the securities at a level above that which might otherwise prevail in the open market. These transactions may be discontinued at any time.

We may engage in at the market offerings into an existing trading market in accordance with Rule 415(a)(4) under the Securities Act. In addition, we may enter into derivative transactions with third parties, or sell securities not covered by this prospectus to third parties in privately negotiated transactions. If the applicable prospectus supplement indicates, in connection with those derivatives, the third parties may sell securities covered by this prospectus and the applicable prospectus supplement, including short sale transactions. If so, the third party may use securities pledged by us or borrowed from us or others to settle those sales or to close out any related open borrowings of stock, and they may use securities received from us in settlement of those derivatives to close out any related open borrowings of stock. The third party in these sale transactions will be an underwriter and will be identified in the applicable prospectus supplement. In addition, we may otherwise loan or pledge securities to a financial institution or other third party that in turn may sell the securities short using this prospectus. The financial institution or other third party may transfer its economic short position to investors in our securities or in connection with a concurrent offering of other securities.

We will file a prospectus supplement to describe the terms of any offering of our securities covered by this prospectus. The prospectus supplement will disclose:

- the terms of the offer;
- the names of any underwriters, including any managing underwriters, as well as any dealers or agents;
- the purchase price of the securities from us;
- the net proceeds to us from the sale of the securities;
- any delayed delivery arrangements;
- any over-allotment or other options under which underwriters, if any, may purchase additional securities from us;
- any underwriting discounts, commissions or other items constituting underwriters' compensation, and any commissions paid to agents;
- in a subscription rights offering, whether we have engaged dealer-managers to facilitate the offering or subscription, including their name or names and compensation;
- any public offering price; and
- other facts material to the transaction.

We will bear all or substantially all of the costs, expenses and fees in connection with the registration of our securities under this prospectus. The underwriters, dealers and agents may engage in transactions with us, or perform services for us, in the ordinary course of business.

In compliance with guidelines of the Financial Industry Regulatory Authority (FINRA), the maximum consideration or discount to be received by any FINRA member or independent broker dealer may not exceed 8% of the aggregate amount of the securities offered pursuant to this prospectus and any applicable prospectus supplement.

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DESCRIPTION OF CAPITAL STOCK

General

We are authorized to issue 130,000,000 shares of all classes of capital stock, of which 125,000,000 shares are common stock, $0.0001 par value per share, and 5,000,000 shares are preferred stock, $0.0001 par value per share. Our capital is stated in U.S. dollars. As of October 31, 2016, we had 21,678,051 outstanding shares of common stock and no outstanding shares of preferred stock.

Common Stock

The holders of our common stock are entitled to receive such dividends or distributions as are lawfully declared on our common stock, to have notice of any authorized meeting of stockholders, and to one vote for each share of our common stock on all matters which are properly submitted to a vote of stockholders. As a Delaware corporation, we are subject to statutory limitations on the declaration and payment of dividends. In the event of a liquidation, dissolution or winding up of our company, holders of our common stock have the right to a ratable portion of assets remaining after satisfaction in full of all outstanding debt and liabilities and the preferential rights and payment of liquidation preferences, if any, on any outstanding shares of preferred stock. The holders of our common stock have no conversion, redemption, preemptive or cumulative voting rights.

Registration Rights

According to the terms of our amended and restated investors' rights agreement entered into in July 2014, certain of our common stockholders are entitled to demand, piggyback and Form S-3 registration rights.

Demand Registration Rights. The holders of at least a majority of the then-outstanding registrable securities may make a written request to us for the registration of any of the registrable securities under the Securities Act, if the amount of registrable securities to be registered would yield an aggregate offering price to the public of at least $10.0 million. Within 90 days of such request, we are obligated to file a registration statement under the Securities Act covering all registrable securities that the initiating holders requested to be registered and any additional registrable securities requested to be included in such registration by any other holders. We are only required to file three registration statements that are declared effective upon exercise of these demand registration rights. We may postpone taking action with respect to such filing once during any 12-month period for a total cumulative period of not more than 90 days if our board of directors determines that the filing would be materially detrimental to us and our stockholders, provided that we do not register any securities for our own account or any other stockholder during such 90-day period (other than a registration relating to employee benefit plans, a registration relating to a corporate reorganization, any registration on any form that does not include substantially the same information as would be required to be included in a registration statement covering the sale of registrable securities or a registration of only common stock issuable upon conversion of debt securities that are also being registered).

Piggyback Registration Rights. If we register any of our securities for public sale, holders of registrable securities will have the right to include their shares in the registration statement. However, this right does not apply to a registration relating to employee benefit plans, a registration relating to a corporate reorganization, any registration on any form that does not include substantially the same information as would be required to be included in a registration statement covering the sale of the registrable securities or a registration of only common stock issuable upon conversion of debt securities that are also being registered. We have the right to terminate any registration we have initiated before the effective date of such registration, whether or not any holder has elected to include registrable securities in such registration. The underwriters of any underwritten offering will have the right to limit the number of shares registered by these holders if they determine in good faith that marketing factors

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require limitation, in which case the number of shares to be registered will be apportioned pro rata among these holders, according to the total amount of securities entitled to be included by each holder, or in a manner mutually agreed upon by the holders. However, the number of shares to be registered by these holders cannot be reduced below 30% of the total shares covered by the registration statement.

Form S-3 Registration Rights. Any holder of then-outstanding registrable securities can request that we register all or part of their shares on Form S-3 if we are eligible to file a registration statement on Form S-3 and if the aggregate price to the public of the shares offered, net of any underwriters' discounts, commissions and other specified offering expenses, is at least $750,000. The stockholders may only require us to effect two registration statements on Form S-3 in a 12-month period. We may postpone taking action with respect to such filing once during any 12-month period for a total cumulative period of not more than 90 days if our board of directors determines that the filing would be detrimental to us and our stockholders, provided that we do not register any securities for our own account or any other stockholder during such 90-day period (other than a registration relating to employee benefit plans, a registration relating to a corporate reorganization, any registration on any form that does not include substantially the same information as would be required to be included in a registration statement covering the sale of registrable securities or a registration of only common stock issuable upon conversion of debt securities that are also being registered).

Expenses of Registration. We generally will pay all expenses, other than underwriting discounts and commissions.

Expiration of Registration Rights. The registration rights described above will expire, with respect to any particular holder of these rights, on the earlier of the seventh anniversary of the closing of our initial public offering, a merger, consolidation, sale or disposition of our company or a sale by a holder of equity securities representing at least a majority of the voting power of our company, or when that holder can sell all of its registrable securities in a three-month period without restriction under Rule 144 of the Securities Act.

Preferred Stock

As of November 2, 2016, no shares of our preferred stock are issued and outstanding and no such shares were subject to outstanding options or other rights to purchase or acquire. However, shares of preferred stock may be issued in one or more series from time to time by our board of directors, and the board of directors is expressly authorized to fix by resolution or resolutions the designations and the powers, preferences and rights, and the qualifications, limitations and restrictions thereof, of the shares of each series of preferred stock. Subject to the determination of our board of directors, any shares of our preferred stock that may be issued in the future would generally have preferences over our common stock with respect to the payment of dividends and the distribution of assets in the event of our liquidation, dissolution or winding up.

Anti-Takeover Effect of Unissued Shares of Capital Stock

Common Stock. Our shares of authorized and unissued common stock are available for future issuance without additional stockholder approval. While these additional shares are not designed to deter or prevent a change of control, under some circumstances we could use the additional shares to create voting impediments or to frustrate persons seeking to effect a takeover or otherwise gain control by, for example, issuing those shares in private placements to purchasers who might side with our board of directors in opposing a hostile takeover bid.

Preferred Stock. Our certificate of incorporation grants our board of directors the authority, without any further vote or action by our stockholders, to issue preferred stock in one or more series

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and to fix the number of shares constituting any such series and the preferences, limitations and relative rights, including dividend rights, dividend rate, voting rights, terms of redemption, redemption price or prices, conversion rights and liquidation preferences of the shares constituting any series. The existence of authorized but unissued preferred stock could reduce our attractiveness as a target for an unsolicited takeover bid since we could, for example, issue shares of preferred stock to parties who might oppose such a takeover bid or shares that contain terms the potential acquirer may find unattractive. This may have the effect of delaying or preventing a change in control, may discourage bids for the common stock at a premium over the market price of the common stock, and may adversely affect the market price of, and the voting and other rights of the holders of, common stock.

Anti-Takeover Provisions

The provisions of Delaware law, our restated certificate of incorporation and our restated bylaws may have the effect of delaying, deferring or discouraging another person from acquiring control of our company.

Delaware Law

We are subject to the provisions of Section 203 of the Delaware General Corporation Law regulating corporate takeovers. This section prevents some Delaware corporations, including us, from engaging, under some circumstances, in a business combination, which includes a merger or sale of at least 10% of the corporation's assets with any interested stockholder, meaning a stockholder who, together with affiliates and associates, owns or, within three years prior to the determination of interested stockholder status, did own 15% or more of the corporation's outstanding voting stock, unless:

- prior to the date of the transaction, the board of directors of the corporation approved either the business combination or the transaction which resulted in the stockholder becoming an interested stockholder;
- upon consummation of the transaction which 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; or
- at or subsequent to such time that the stockholder became an interested stockholder, the business combination is approved by the board of directors and authorized at an annual or special meeting of stockholders by at least two-thirds of the outstanding voting stock not owned by the interested stockholder.

A Delaware corporation may "opt out" of these provisions with an express provision in its original certificate of incorporation or an express provision in its certificate of incorporation or bylaws resulting from a stockholders' amendment approved by at least a majority of the outstanding voting shares. We have not and do not plan to "opt out" of these provisions. The statute could prohibit or delay mergers or other takeover or change in control attempts and, accordingly, may discourage attempts to acquire us.

Restated Certificate of Incorporation and Restated Bylaw Provisions

Our restated certificate of incorporation and our restated bylaws include a number of provisions that may have the effect of deterring hostile takeovers or delaying or preventing changes in control, including the following:

Board of Directors Vacancies. Our restated certificate of incorporation and restated bylaws authorize only our board of directors to fill vacant directorships, including newly created seats unless our board of directors determines by resolution that such vacancies be filled by stockholders

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or as otherwise provided by law. In addition, the number of directors constituting our board of directors is permitted to be set only by a resolution adopted by a majority vote of our entire board of directors. These provisions would prevent a stockholder from increasing the size of our board of directors and then gaining control of our board of directors by filling the resulting vacancies with its own nominees. This makes it more difficult to change the composition of our board of directors but promotes continuity of management.

Classified Board. Our restated certificate of incorporation and restated bylaws provide that our board is classified into three classes of directors, each with staggered three-year terms. A third party may be discouraged from making a tender offer or otherwise attempting to obtain control of us as it is more difficult and time consuming for stockholders to replace a majority of the directors on a classified board of directors.

Stockholder Action; Special Meetings of Stockholders. Our restated certificate of incorporation provides that our stockholders may not take action by written consent, but may only take action at annual or special meetings of our stockholders. As a result, a holder controlling a majority of our capital stock would not be able to amend our restated bylaws or remove directors without holding a meeting of our stockholders called in accordance with our restated bylaws. Further, our restated bylaws provide that special meetings of our stockholders may be called only by a majority of our board of directors, the chairman of our board of directors, the lead independent director, our Chief Executive Officer or our President, thus prohibiting a stockholder from calling a special meeting. These provisions might delay the ability of our stockholders to force consideration of a proposal or for stockholders controlling a majority of our capital stock to take any action, including the removal of directors.

Advance Notice Requirements for Stockholder Proposals and Director Nominations. Our restated bylaws provide advance notice procedures for stockholders seeking to bring business before our annual meeting of stockholders or to nominate candidates for election as directors at our annual meeting of stockholders. Our restated bylaws also specify certain requirements regarding the form and content of a stockholder's notice. These provisions might preclude our stockholders from bringing matters before our annual meeting of stockholders or from making nominations for directors at our annual meeting of stockholders if the proper procedures are not followed. We expect that these provisions might also discourage or deter a potential acquirer from conducting a solicitation of proxies to elect the acquirer's own slate of directors or otherwise attempting to obtain control of our company.

No Cumulative Voting. The Delaware General Corporation Law provides that stockholders are not entitled to the right to cumulate votes in the election of directors unless a corporation's certificate of incorporation provides otherwise. Our restated certificate of incorporation and restated bylaws do not provide for cumulative voting.

Directors Removed Only for Cause. Our restated certificate of incorporation provides that stockholders may remove directors only for cause and only by the affirmative vote of a majority of holders of our capital stock permitted to vote on the election of directors.

Amendment of Charter Provisions. Any amendment of the above expected provisions in our restated certificate of incorporation requires approval by holders of at least two-thirds of our outstanding common stock, provided that if two-thirds of our board of directors approves such an amendment, then only the approval of a majority of holders is required.

Issuance of Undesignated Preferred Stock. Our board of directors has the authority, without further action by the stockholders, to issue up to 5,000,000 shares of undesignated preferred stock with rights and preferences, including voting rights, designated from time to time by our board of

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directors. The existence of authorized but unissued shares of preferred stock would enable our board of directors to render more difficult or to discourage an attempt to obtain control of us by merger, tender offer, proxy contest or other means.

Choice of Forum. Our restated certificate of incorporation provides that unless we consent in writing to the selection of an alternative forum, the Court of Chancery of the State of Delaware will be the exclusive forum for any derivative action or proceeding brought on our behalf; any action asserting a breach of fiduciary duty; any action asserting a claim against us arising pursuant to the Delaware General Corporation Law, our restated certificate of incorporation or our restated bylaws; or any action asserting a claim against us that is governed by the internal affairs doctrine.

Transfer Agent and Registrar

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

Listing

Our common stock is quoted on the NASDAQ Global Market under the trading symbol "LOXO."

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DESCRIPTION OF DEBT SECURITIES

General

We will issue the debt securities offered by this prospectus and any accompanying prospectus supplement under an indenture to be entered into between us and the trustee identified in the applicable prospectus supplement. The terms of the debt securities will include those stated in the indenture and those made part of the indenture by reference to the Trust Indenture Act of 1939, as in effect on the date of the indenture. We have filed a copy of the form of indenture as an exhibit to the registration statement in which this prospectus is included. The indenture will be subject to and governed by the terms of the Trust Indenture Act of 1939.

We may offer under this prospectus up to an aggregate principal amount of $250,000,000 in debt securities, or if debt securities are issued at a discount, or in a foreign currency, foreign currency units or composite currency, the principal amount as may be sold for an aggregate public offering price of up to $250,000,000. Unless otherwise specified in the applicable prospectus supplement, the debt securities will represent our direct, unsecured obligations and will rank equally with all of our other unsecured indebtedness.

We may issue the debt securities in one or more series with the same or various maturities, at par, at a premium, or at a discount. We will describe the particular terms of each series of debt securities in a prospectus supplement relating to that series, which we will file with the SEC. The prospectus supplement relating to the particular series of debt securities being offered will specify the particular amounts, prices and terms of those debt securities. These terms may include:

- the title of the series;
- the aggregate principal amount, and, if a series, the total amount authorized and the total amount outstanding;
- the issue price or prices, expressed as a percentage of the aggregate principal amount of the debt securities;
- any limit on the aggregate principal amount;
- the date or dates on which principal is payable;
- the interest rate or rates (which may be fixed or variable) or, if applicable, the method used to determine such rate or rates;
- the date or dates from which interest, if any, will be payable and any regular record date for the interest payable;
- the place or places where principal and, if applicable, premium and interest, is payable;
- the terms and conditions upon which we may, or the holders may require us to, redeem or repurchase the debt securities;
- the denominations in which such debt securities may be issuable, if other than denominations of $1,000 or any integral multiple of that number;
- whether the debt securities are to be issuable in the form of certificated securities (as described below) or global securities (as described below);
- the portion of principal amount that will be payable upon declaration of acceleration of the maturity date if other than the principal amount of the debt securities;
- the currency of denomination;

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- the designation of the currency, currencies or currency units in which payment of principal and, if applicable, premium and interest, will be made;
- if payments of principal and, if applicable, premium or interest, on the debt securities are to be made in one or more currencies or currency units other than the currency of denomination, the manner in which the exchange rate with respect to such payments will be determined;
- if amounts of principal and, if applicable, premium and interest may be determined by reference to an index based on a currency or currencies or by reference to a commodity, commodity index, stock exchange index or financial index, then the manner in which such amounts will be determined;
- the provisions, if any, relating to any collateral provided for such debt securities;
- any addition to or change in the covenants and/or the acceleration provisions described in this prospectus or in the indenture;
- any events of default, if not otherwise described below under "Events of Default";
- the terms and conditions, if any, for conversion into or exchange for shares of our common stock or preferred stock;
- any depositaries, interest rate calculation agents, exchange rate calculation agents or other agents; and
- the terms and conditions, if any, upon which the debt securities shall be subordinated in right of payment to our other indebtedness.

We may issue discount debt securities that provide for an amount less than the stated principal amount to be due and payable upon acceleration of the maturity of such debt securities in accordance with the terms of the indenture. We may also issue debt securities in bearer form, with or without coupons. If we issue discount debt securities or debt securities in bearer form, we will describe material U.S. federal income tax considerations and other material special considerations which apply to these debt securities in the applicable prospectus supplement.

We may issue debt securities denominated in or payable in a foreign currency or currencies or a foreign currency unit or units. If we do, we will describe the restrictions, elections, and general tax considerations relating to the debt securities and the foreign currency or currencies or foreign currency unit or units in the applicable prospectus supplement.

Debt securities offered under this prospectus and any prospectus supplement will be subordinated in right of payment to certain of our outstanding senior indebtedness. In addition, we will seek the consent of the holders of any such senior indebtedness prior to issuing any debt securities under this prospectus to the extent required by the agreements evidencing such senior indebtedness.

Registrar and Paying Agent

The debt securities may be presented for registration of transfer or for exchange at the corporate trust office of the security registrar or at any other office or agency that we maintain for those purposes. In addition, the debt securities may be presented for payment of principal, interest and any premium at the office of the paying agent or at any office or agency that we maintain for those purposes.

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Conversion or Exchange Rights

Debt securities may be convertible into or exchangeable for shares of our common stock. The terms and conditions of conversion or exchange will be stated in the applicable prospectus supplement. The terms will include, among others, the following:

- the conversion or exchange price;
- the conversion or exchange period;
- provisions regarding the convertibility or exchangeability of the debt securities, including who may convert or exchange;
- events requiring adjustment to the conversion or exchange price;
- provisions affecting conversion or exchange in the event of our redemption of the debt securities; and
- any anti-dilution provisions, if applicable.

Registered Global Securities

If we decide to issue debt securities in the form of one or more global securities, then we will register the global securities in the name of the depositary for the global securities or the nominee of the depositary, and the global securities will be delivered by the trustee to the depositary for credit to the accounts of the holders of beneficial interests in the debt securities.

The prospectus supplement will describe the specific terms of the depositary arrangement for debt securities of a series that are issued in global form. None of us, the trustee, any payment agent or the security registrar will have any responsibility or liability for any aspect of the records relating to or payments made on account of beneficial ownership interests in a global debt security or for maintaining, supervising or reviewing any records relating to these beneficial ownership interests.

No Protection in the Event of Change of Control

The indenture does not have any covenants or other provisions providing for a put or increased interest or otherwise that would afford holders of our debt securities additional protection in the event of a recapitalization transaction, a change of control or a highly leveraged transaction. If we offer any covenants or provisions of this type with respect to any debt securities covered by this prospectus, we will describe them in the applicable prospectus supplement.

Covenants

Unless otherwise indicated in this prospectus or the applicable prospectus supplement, our debt securities will not have the benefit of any covenants that limit or restrict our business or operations, the pledging of our assets or the incurrence by us of indebtedness. We will describe in the applicable prospectus supplement any material covenants in respect of a series of debt securities.

Merger, Consolidation or Sale of Assets

The form of indenture provides that we will not consolidate with or merge into any other person or convey, transfer, sell or lease our properties and assets substantially as an entirety to any person, unless:

- we are the surviving person of such merger or consolidation, or if we are not the surviving person, the person formed by the consolidation or into or with which we are merged or the person to which our properties and assets are conveyed, transferred, sold or leased, is a

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corporation organized and existing under the laws of the U.S., any state or the District of Columbia or a corporation or comparable legal entity organized under the laws of a foreign jurisdiction and has expressly assumed all of our obligations, including the payment of the principal of and, premium, if any, and interest on the debt securities and the performance of the other covenants under the indenture; and

- immediately before and immediately after giving effect to the transaction on a pro forma basis, no event of default, and no event which, after notice or lapse of time or both, would become an event of default, has occurred and is continuing under the indenture.

Events of Default

Unless otherwise specified in the applicable prospectus supplement, the following events will be events of default under the indenture with respect to debt securities of any series:

- we fail to pay any principal or premium, if any, when it becomes due;
- we fail to pay any interest within 30 days after it becomes due;
- we fail to observe or perform any other covenant in the debt securities or the indenture for 60 days after written notice specifying the failure from the trustee or the holders of not less than 25% in aggregate principal amount of the outstanding debt securities of that series; and
- certain events involving bankruptcy, insolvency or reorganization of us or any of our significant subsidiaries.

The trustee may withhold notice to the holders of the debt securities of any series of any default, except in payment of principal of or premium, if any, or interest on the debt securities of a series, if the trustee considers it to be in the best interest of the holders of the debt securities of that series to do so.

If an event of default (other than an event of default resulting from certain events of bankruptcy, insolvency or reorganization) occurs, and is continuing, then the trustee or the holders of not less than 25% in aggregate principal amount of the outstanding debt securities of any series may accelerate the maturity of the debt securities. If this happens, the entire principal amount, plus the premium, if any, of all the outstanding debt securities of the affected series plus accrued interest to the date of acceleration will be immediately due and payable. At any time after the acceleration, but before a judgment or decree based on such acceleration is obtained by the trustee, the holders of a majority in aggregate principal amount of outstanding debt securities of such series may rescind and annul such acceleration if:

- all events of default (other than nonpayment of accelerated principal, premium or interest) have been cured or waived;
- all lawful interest on overdue interest and overdue principal has been paid; and
- the rescission would not conflict with any judgment or decree.

In addition, if the acceleration occurs at any time when we have outstanding indebtedness that is senior to the debt securities, the payment of the principal amount of outstanding debt securities may be subordinated in right of payment to the prior payment of any amounts due under the senior indebtedness, in which case the holders of debt securities will be entitled to payment under the terms prescribed in the instruments evidencing the senior indebtedness and the indenture.

If an event of default resulting from certain events of bankruptcy, insolvency or reorganization occurs, the principal, premium and interest amount with respect to all of the debt securities of any

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series will be due and payable immediately without any declaration or other act on the part of the trustee or the holders of the debt securities of that series.

The holders of a majority in principal amount of the outstanding debt securities of a series will have the right to waive any existing default or compliance with any provision of the indenture or the debt securities of that series and to direct the time, method and place of conducting any proceeding for any remedy available to the trustee, subject to certain limitations specified in the indenture.

No holder of any debt security of a series will have any right to institute any proceeding with respect to the indenture or for any remedy under the indenture, unless:

- the holder gives to the trustee written notice of a continuing event of default;
- the holders of at least 25% in aggregate principal amount of the outstanding debt securities of the affected series make a written request and offer reasonable indemnity to the trustee to institute a proceeding as trustee;
- the trustee fails to institute a proceeding within 60 days after such request; and
- the holders of a majority in aggregate principal amount of the outstanding debt securities of the affected series do not give the trustee a direction inconsistent with such request during such 60-day period.

These limitations do not, however, apply to a suit instituted for payment on debt securities of any series on or after the due dates expressed in the debt securities.

We will periodically deliver certificates to the trustee regarding our compliance with our obligations under the indenture.

Modification and Waiver

From time to time, we and the trustee may, without the consent of holders of the debt securities of one or more series, amend the indenture or the debt securities of one or more series, or supplement the indenture, for certain specified purposes, including:

- to provide that the surviving entity following a change of control permitted under the indenture will assume all of our obligations under the indenture and debt securities;
- to provide for certificated debt securities in addition to uncertificated debt securities;
- to comply with any requirements of the SEC under the Trust Indenture Act of 1939;
- to provide for the issuance of and establish the form and terms and conditions of debt securities of any series as permitted by the indenture;
- to cure any ambiguity, defect or inconsistency, or make any other change that does not materially and adversely affect the rights of any holder; and
- to appoint a successor trustee under the indenture with respect to one or more series.

From time to time we and the trustee may, with the consent of holders of at least a majority in principal amount of an outstanding series of debt securities, amend or supplement the indenture or the debt securities series, or waive compliance in a particular instance by us with any provision of the indenture or the debt securities. We may not, however, without the consent of each holder affected by such action, modify or supplement the indenture or the debt securities or waive compliance with any provision of the indenture or the debt securities in order to:

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reduce the amount of debt securities whose holders must consent to an amendment, supplement, or waiver to the indenture or such debt security;

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- reduce the rate of or change the time for payment of interest or reduce the amount of or postpone the date for payment of sinking fund or analogous obligations;
- reduce the principal of or change the stated maturity of the debt securities;
- make any debt security payable in money other than that stated in the debt security;
- change the amount or time of any payment required or reduce the premium payable upon any redemption, or change the time before which no such redemption may be made;
- waive a default in the payment of the principal of, premium, if any, or interest on the debt securities or a redemption payment;
- waive a redemption payment with respect to any debt securities or change any provision with respect to redemption of debt securities; or
- take any other action otherwise prohibited by the indenture to be taken without the consent of each holder affected by the action.

Defeasance of Debt Securities and Certain Covenants in Certain Circumstances

The indenture permits us, at any time, to elect to discharge our obligations with respect to one or more series of debt securities by following certain procedures described in the indenture. These procedures will allow us either:

- to defease and be discharged from any and all of our obligations with respect to any debt securities except for the following obligations (which discharge is referred to as "legal defeasance"):

  1. to register the transfer or exchange of such debt securities;
  2. to replace temporary or mutilated, destroyed, lost or stolen debt securities;
  3. to compensate and indemnify the trustee; or
  4. to maintain an office or agency in respect of the debt securities and to hold monies for payment in trust; or

- to be released from our obligations with respect to the debt securities under certain covenants contained in the indenture, as well as any additional covenants which may be contained in the applicable supplemental indenture (which release is referred to as "covenant defeasance").

In order to exercise either defeasance option, we must irrevocably deposit with the trustee or other qualifying trustee, in trust for that purpose:

- money;
- U.S. Government Obligations (as described below) or Foreign Government Obligations (as described below) that through the scheduled payment of principal and interest in accordance with their terms will provide money; or
- a combination of money and/or U.S. Government Obligations and/or Foreign Government Obligations sufficient in the written opinion of a nationally-recognized firm of independent accountants to provide money;

that, in each case specified above, provides a sufficient amount to pay the principal of, premium, if any, and interest, if any, on the debt securities of the series, on the scheduled due dates or on a selected date of redemption in accordance with the terms of the indenture.

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In addition, defeasance may be effected only if, among other things:

- in the case of either legal or covenant defeasance, we deliver to the trustee an opinion of counsel, as specified in the indenture, stating that as a result of the defeasance neither the trust nor the trustee will be required to register as an investment company under the Investment Company Act of 1940;

- in the case of legal defeasance, we deliver to the trustee an opinion of counsel stating that we have received from, or there has been published by, the Internal Revenue Service a ruling to the effect that, or there has been a change in any applicable federal income tax law with the effect that (and the opinion shall confirm that), the holders of outstanding debt securities will not recognize income, gain or loss for U.S. federal income tax purposes solely as a result of such legal defeasance and will be subject to U.S. federal income tax on the same amounts, in the same manner, including as a result of prepayment, and at the same times as would have been the case if legal defeasance had not occurred;

- in the case of covenant defeasance, we deliver to the trustee an opinion of counsel to the effect that the holders of the outstanding debt securities will not recognize income, gain or loss for U.S. federal income tax purposes as a result of covenant defeasance and will be subject to U.S. federal income tax on the same amounts, in the same manner and at the same times as would have been the case if covenant defeasance had not occurred; and

- certain other conditions described in the indenture are satisfied.

If we fail to comply with our remaining obligations under the indenture and applicable supplemental indenture after a covenant defeasance of the indenture and applicable supplemental indenture, and the debt securities are declared due and payable because of the occurrence of any undefeased event of default, the amount of money and/or U.S. Government Obligations and/or Foreign Government Obligations on deposit with the trustee could be insufficient to pay amounts due under the debt securities of the affected series at the time of acceleration. We will, however, remain liable in respect of these payments.

The term "U.S. Government Obligations" as used in the above discussion means securities that are direct obligations of or non-callable obligations guaranteed by the United States of America for the payment of which obligation or guarantee the full faith and credit of the United States of America is pledged.

The term "Foreign Government Obligations" as used in the above discussion means, with respect to debt securities of any series that are denominated in a currency other than U.S. dollars, (1) direct obligations of the government that issued or caused to be issued such currency for the payment of which obligations its full faith and credit is pledged or (2) obligations of a person controlled or supervised by or acting as an agent or instrumentality of such government the timely payment of which is unconditionally guaranteed as a full faith and credit obligation by that government, which in either case under clauses (1) or (2), are not callable or redeemable at the option of the issuer.

Regarding the Trustee

We will identify the trustee with respect to any series of debt securities in the prospectus supplement relating to the applicable debt securities. You should note that if the trustee becomes a creditor of ours, the indenture and the Trust Indenture Act of 1939 limit the rights of the trustee to obtain payment of claims in certain cases, or to realize on certain property received in respect of any such claim, as security or otherwise. The trustee and its affiliates may engage in, and will be permitted to continue to engage in, other transactions with us and our affiliates. If, however, the trustee acquires any "conflicting interest" within the meaning of the Trust Indenture Act of 1939, it must eliminate such conflict or resign.

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The holders of a majority in principal amount of the then outstanding debt securities of any series may direct the time, method and place of conducting any proceeding for exercising any remedy available to the trustee. If an event of default occurs and is continuing, the trustee, in the exercise of its rights and powers, must use the degree of care and skill of a prudent person in the conduct of his or her own affairs. Subject to that provision, the trustee will be under no obligation to exercise any of its rights or powers under the indenture at the request of any of the holders of the debt securities, unless they have offered to the trustee reasonable indemnity or security.

No Individual Liability of Incorporators, Stockholders, Officers or Directors

Each indenture provides that no incorporator and no past, present or future stockholder, officer or director of our company or any successor corporation in those capacities will have any individual liability for any of our obligations, covenants or agreements under the debt securities or such indenture.

Governing Law

The indentures and the debt securities will be governed by, and construed in accordance with, the laws of the State of New York.

DESCRIPTION OF WARRANTS

General

We may issue warrants for the purchase of our debt securities, preferred stock, common stock, or any combination thereof. Warrants may be issued independently or together with our debt securities, preferred stock or common stock and may be attached to or separate from any offered securities. Each series of warrants will be issued under a separate warrant agreement to be entered into between us and a bank or trust company, as warrant agent. The warrant agent will act solely as our agent in connection with the warrants. The warrant agent will not have any obligation or relationship of agency or trust for or with any holders or beneficial owners of warrants. This summary of certain provisions of the warrants is not complete. For the terms of a particular series of warrants, you should refer to the prospectus supplement for that series of warrants and the warrant agreement for that particular series.

Debt Warrants

The prospectus supplement relating to a particular issue of warrants to purchase debt securities will describe the terms of the debt warrants, including the following:

- the title of the debt warrants;
- the offering price for the debt warrants, if any;
- the aggregate number of the debt warrants;
- the designation and terms of the debt securities, including any conversion rights, purchasable upon exercise of the debt warrants;
- if applicable, the date from and after which the debt warrants and any debt securities issued with them will be separately transferable;
- the principal amount of debt securities that may be purchased upon exercise of a debt warrant and the exercise price for the warrants, which may be payable in cash, securities or other property;
- the dates on which the right to exercise the debt warrants will commence and expire;

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- if applicable, the minimum or maximum amount of the debt warrants that may be exercised at any one time;
- whether the debt warrants represented by the debt warrant certificates or debt securities that may be issued upon exercise of the debt warrants will be issued in registered or bearer form;
- information with respect to book-entry procedures, if any;
- the currency or currency units in which the offering price, if any, and the exercise price are payable;
- if applicable, a discussion of material U.S. federal income tax considerations;
- the antidilution provisions of the debt warrants, if any;
- the redemption or call provisions, if any, applicable to the debt warrants;
- any provisions with respect to the holder's right to require us to repurchase the debt warrants upon a change in control or similar event; and
- any additional terms of the debt warrants, including procedures and limitations relating to the exchange, exercise, and settlement of the debt warrants.

Debt warrant certificates will be exchangeable for new debt warrant certificates of different denominations. Debt warrants may be exercised at the corporate trust office of the warrant agent or any other office indicated in the prospectus supplement. Prior to the exercise of their debt warrants, holders of debt warrants will not have any of the rights of holders of the debt securities purchasable upon exercise and will not be entitled to payment of principal or any premium, if any, or interest on the debt securities purchasable upon exercise.

Equity Warrants

The prospectus supplement relating to a particular series of warrants to purchase our common stock or preferred stock will describe the terms of the warrants, including the following:

- the title of the warrants;
- the offering price for the warrants, if any;
- the aggregate number of warrants;
- the designation and terms of the common stock or preferred stock that may be purchased upon exercise of the warrants;
- if applicable, the designation and terms of the securities with which the warrants are issued and the number of warrants issued with each security;
- if applicable, the date from and after which the warrants and any securities issued with the warrants will be separately transferable;
- the number of shares of common stock or preferred stock that may be purchased upon exercise of a warrant and the exercise price for the warrants;
- the dates on which the right to exercise the warrants shall commence and expire;
- if applicable, the minimum or maximum amount of the warrants that may be exercised at any one time;
- the currency or currency units in which the offering price, if any, and the exercise price are payable;

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- if applicable, a discussion of material U.S. federal income tax considerations;
- the antidilution provisions of the warrants, if any;
- the redemption or call provisions, if any, applicable to the warrants;
- any provisions with respect to a holder's right to require us to repurchase the warrants upon a change in control or similar event; and
- any additional terms of the warrants, including procedures and limitations relating to the exchange, exercise and settlement of the warrants.

Holders of equity warrants will not be entitled:

- to vote, consent, or receive dividends;
- receive notice as stockholders with respect to any meeting of stockholders for the election of our directors or any other matter; or
- exercise any rights as stockholders.

DESCRIPTION OF SUBSCRIPTION RIGHTS

We may issue subscription rights to purchase our common stock, preferred stock or debt securities. These subscription rights may be offered independently or together with any other security offered hereby and may or may not be transferable by the stockholder receiving the subscription rights in such offering. In connection with any offering of subscription rights, we may enter into a standby arrangement with one or more underwriters or other purchasers pursuant to which the underwriters or other purchasers may be required to purchase any securities remaining unsubscribed for after such offering.

The prospectus supplement relating to any subscription rights we offer, if any, will, to the extent applicable, include specific terms relating to the offering, including some or all of the following:

- the price, if any, for the subscription rights;
- the exercise price payable for our common stock, preferred stock or debt securities upon the exercise of the subscription rights;
- the number of subscription rights to be issued to each stockholder;
- the number and terms of our common stock, preferred stock or debt securities which may be purchased per each subscription right;
- the extent to which the subscription rights are transferable;
- any other terms of the subscription rights, including the terms, procedures and limitations relating to the exchange and exercise of the subscription rights;
- the date on which the right to exercise the subscription rights shall commence, and the date on which the subscription rights shall expire;
- the extent to which the subscription rights may include an over-subscription privilege with respect to unsubscribed securities or an over-allotment privilege to the extent the securities are fully subscribed; and
- if applicable, the material terms of any standby underwriting or purchase arrangement which may be entered into by us in connection with the offering of subscription rights.

The description in the applicable prospectus supplement of any subscription rights we offer will not necessarily be complete and will be qualified in its entirety by reference to the applicable subscription

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rights certificate, which will be filed with the SEC if we offer subscription rights. We urge you to read the applicable subscription rights certificate and any applicable prospectus supplement in their entirety.

DESCRIPTION OF UNITS

We may issue units consisting of some or all of the securities described above, in any combination, including common stock, preferred stock, warrants and/or debt securities. The terms of these units will be set forth in a prospectus supplement. The description of the terms of these units in the related prospectus supplement will not be complete. You should refer to the applicable form of unit and unit agreement for complete information with respect to these units.

LEGAL MATTERS

Fenwick & West LLP, Mountain View, California, will issue an opinion about certain legal matters with respect to the securities. Any underwriters or agents will be advised about legal matters relating to any offering by their own counsel.

EXPERTS

The financial statements incorporated in this Prospectus by reference from the Company's Annual Report on Form 10-K have been audited by CohnReznick LLP, independent registered public accounting firm, as stated in its report, which is incorporated herein by reference. Such financial statements have been so incorporated in reliance upon the report of such firm given upon its authority as experts in accounting and auditing.

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3,870,000 Shares

Loxo Oncology, Inc.

Common Stock

PROSPECTUS SUPPLEMENT

Joint Book-Running Managers

Morgan Stanley **Citigroup** **Cowen and Company**

Lead Manager

Stifel

January 4, 2017