Tocagen™

No One Should Die Of Cancer™

Closing out a successful year, Tocagen was invited to ring the Nasdaq closing bell on Jan. 22. The highlight was seeing videos of our clinical trial patients on the big screen in Times Square.

2018 Annual Report

TO OUR SHAREHOLDERS

At Tocagen, we are fueled by the inspiration we gain from patients. Throughout 2018, we drew from this inspiration to achieve significant milestones, taking us closer to our goal of bringing new hope and potentially transformative treatments to help patients fight their cancer.

In 2018, Tocagen also physically moved — expanding into a larger San Diego-based facility that can accommodate our planned growth as we build towards commercialization and advance our cutting-edge science and cancer-selective gene therapy platform. We ended the year in a favorable financial position, which will enable us to execute our 2019 goals, including unveiling results from our Phase 3 Toca 5 trial, and setting us up for success going into 2020.

AMONG THE MANY ACHIEVEMENTS FROM OUR DEDICATED TEAM AT TOCAGEN, HERE ARE SIX EXAMPLES:

- The first interim analysis of data from our pivotal Phase 3 Toca 5 trial provided the expected "continue without modification" and we now look towards the planned second interim analysis in the first half of 2019 and final analysis by the end of 2019.
- We completed the planned enrollment of 380 patients in the Toca 5 trial approximately three months ahead of schedule, a testament to the enthusiasm and dedication of our investigators and study coordinators, as well as the patients, families and patient advocates who have made this study possible.
- Under our PRIME (PRIority MEdicines) designation for Toca 511 & Toca FC, the European Medicines Agency indicated that the statistical analyses, seamless design and use of overall survival as the primary endpoint in the ongoing Phase 3 Toca 5 clinical trial are appropriate for a potential marketing authorization application for Toca 511 & Toca FC in Europe. In addition, NRG Oncology, a member of the National Cancer Institute's National Clinical Trial Network, announced plans to evaluate Toca 511 & Toca FC for the treatment of patients with newly diagnosed glioblastoma (GBM).
- With our strategic hire of Mohamed Ladha as vice president and commercial head, we are quickly progressing our preparations for the potential US commercial launch of Toca 511 & Toca FC in recurrent GBM.
- We bolstered our financial position, concluding 2018 with approximately $96 million in cash and cash equivalents. Earlier in the year, we restructured our venture debt and entered into an amended agreement to defer further principal amortization until 2020. These efforts added some $18 million to our cash reserve. In addition, we entered into a license agreement with ApolloBio to develop and commercialize Toca 511 & Toca FC in the Greater China Region. ApolloBio made upfront and milestone payments totaling $18 million in 2018, and we will be eligible for additional future payments of up to $109 million.
- Lastly, in December we completed a secondary public offering of 3,000,000 shares of common stock at a price of $10.00 per share. Net proceeds from the offering were approximately $28 million after deducting underwriting discounts, commissions and offering expenses.

As we look towards 2019 and beyond, I and the rest of the Tocagen management team feel tremendous momentum, excitement and hope for the patients we serve. Thank you for joining us on our mission.

Sincerely,

Marty J. Duvall
Chief Executive Officer

Tocagen

UNITED STATES
SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

FORM 10-K

(Mark One)

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

For the fiscal year ended December 31, 2018

OR

☐ **TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**
FOR THE TRANSITION PERIOD FROM TO

Commission File Number 001-38052

TOCAGEN INC.

(Exact name of registrant as specified in its Charter)

Delaware	**26-1243872**
State or other jurisdiction of incorporation or organization)	**(I.R.S. Employer Identification No.)**
4242 Campus Point Court, Suite 500 San Diego, CA	**92121**
(Address of principal executive offices)	**(Zip Code)**

Registrant's telephone number, including area code: (858) 412-8400

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

Title of each class	Name of each exchange on which registered
Common Stock, par value $0.001 per share	The Nasdaq Global Select Market

Securities registered pursuant to 12(g) of the Act: None

Indicate by check mark if the registrant is a well-known seasoned issuer, as defined in Rule 405 of the Securities Act. YES ☐ NO ☒

Indicate by check mark if the registrant is not required to file reports pursuant to Section 13 or 15(d) of the Act. YES ☐ NO ☒

Indicate by check mark whether the registrant: (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days. YES ☒ NO ☐

Indicate by check mark whether the registrant has submitted electronically every Interactive Data File required to be submitted pursuant to Rule 405 of Regulation S-T (§232.405 of this chapter) during the preceding 12 months (or for such shorter period that the registrant was required to submit such files). YES ☒ NO ☐

Indicate by check mark if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K (§229.405) is not contained herein, and will not be contained, to the best of registrant's knowledge, in definitive proxy or information statements incorporated by reference in Part III of this Form 10-K or any amendment to this Form 10-K. ☒

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, smaller reporting company, or an emerging growth company. See the definitions of "large accelerated filer," "accelerated filer," "smaller reporting company," and "emerging growth company" in Rule 12b-2 of the Exchange Act.

Large accelerated filer	☐	Accelerated filer	☒
Non-accelerated filer	☐	Smaller reporting company	☒
Emerging growth company	☒		

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act. ☒

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

The aggregate market value of the voting and non-voting common equity held by non-affiliates of the registrant as of June 30, 2018 (the last business day of the registrant's most recently completed second fiscal quarter) was approximately $186 million based on the closing price of the registrant's common stock on June 30, 2018 of $9.34 per share, as reported by the Nasdaq Global Select Market.

As of February 22, 2019, there were 23,019,097 shares of the registrant's common stock outstanding.

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the registrant's definitive proxy statement to be filed with the Securities and Exchange Commission, or SEC, subsequent to the date hereof pursuant to Regulation 14A in connection with the registrant's 2019 Annual Meeting of Stockholders, are incorporated by reference into Part III of this Annual Report on Form 10-K. Such proxy statement will be filed with the SEC not later than 120 days after the conclusion of the registrant's fiscal year ended December 31, 2018.

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SPECIAL NOTE REGARDING FORWARD-LOOKING STATEMENTS

This Annual Report on Form 10-K contains forward-looking statements. The forward-looking statements are contained principally in the sections entitled "Risk Factors," "Management's Discussion and Analysis of Financial Condition and Results of Operations" and "Business." These statements relate to future events or to our future financial performance and involve known and unknown risks, uncertainties and other factors which may cause our actual results, performance or achievements to be materially different from any future results, performance or achievements expressed or implied by the forward-looking statements. Forward-looking statements include, but are not limited to, statements about:

- the success, cost, timing and potential indications of our product development activities and clinical trials, including our ongoing clinical trials and manufacturing of Toca 511 & Toca FC;
- our ability to obtain and maintain regulatory approval of our product candidates, including Toca 511 & Toca FC, in any of the indications for which we plan to develop them, and any related restrictions, limitations, and/or warnings in the label of an approved product candidate;
- our ability to obtain funding for our operations, including funding necessary to complete the clinical trials of any of our product candidates, including Toca 511 & Toca FC;
- our plans to research, develop and commercialize our product candidates, including Toca 511 & Toca FC;
- our ability to attract and retain collaborators with development, regulatory and commercialization expertise;
- the size of the markets for our product candidates, and our ability to serve those markets;
- our ability to successfully commercialize our product candidates, including Toca 511 & Toca FC;
- the rate and degree of market acceptance of our product candidates, including Toca 511 & Toca FC;
- our ability to develop and maintain sales and marketing capabilities, whether alone or with potential future collaborators;
- regulatory developments in the United States and foreign countries;
- the performance of our third-party suppliers and manufacturers;
- the success of competing therapies that are or become available;
- our ability to attract and retain key scientific or management personnel;
- our expectations regarding the period during which we qualify as an emerging growth company under the Jumpstart Our Business Startups Act, or JOBS Act;
- the accuracy of our estimates regarding expenses, future revenues, capital requirements and needs for additional financing; and
- our expectations regarding our ability to obtain and maintain intellectual property protection for our product candidates and our ability to operate our business without infringing on the intellectual property rights of others.

In some cases, you can identify these statements by terms such as "anticipate," "believe," "could," "estimate," "expects," "intend," "may," "plan," "potential," "predict," "project," "should," "will," "would" or the negative of those terms, and similar expressions that convey uncertainty of future events or outcomes. These forward-looking statements reflect our management's beliefs, opinions and views with respect to future events and are based on estimates, assumptions and information available to us as of the date of this Annual Report on Form 10-K, and while we believe such information forms a reasonable basis for such statements, such information may be limited or incomplete and our statements should not be read to indicate that we have conducted an exhaustive inquiry into, or review of, all potentially available relevant information. These statements are inherently uncertain and are subject to risks and uncertainties. We discuss many of these risks in greater detail under the heading "Risk Factors." Moreover, we operate in a very competitive and rapidly changing environment. New risks emerge from time to time. It is not possible for our management to predict all risks, nor can we assess the impact of all factors on our business or the extent to which any factor, or combination of factors, may cause actual results to differ materially from those contained in any forward-looking statements we may make. Given these uncertainties, you should not place undue reliance on these forward-looking statements.

You should carefully read this Annual Report on Form 10-K and the documents that we reference herein and have filed as exhibits to the Annual Report on Form 10-K completely and with the understanding that our actual future results may be materially different from what we expect. We qualify all of the forward-looking statements in this Annual Report on Form 10-K by these cautionary statements.

Except as required by law, we assume no obligation to update these forward-looking statements publicly, or to update the reasons actual results could differ materially from those anticipated in any forward-looking statements, whether as a result of new information, future events or otherwise.

PART I

Item 1. Business.

Overview

We are a clinical-stage, cancer-selective gene therapy company focused on developing first-in-class, broadly-applicable product candidates designed to activate a patient's immune system against their own cancer. Our cancer-selective gene therapy platform is built on Retroviral Replicating Vectors, or RRVs, which are designed to selectively deliver therapeutic genes into the DNA of cancer cells. Our gene therapy approach is designed to fight cancer through immunotherapeutic mechanisms of action without the autoimmune toxicities commonly experienced with other immunotherapies. Our founding vision is "No One Should Die Of Cancer" because we believe the immune system can be safely activated to fight the patient's cancer.

We are developing our lead product candidate, Toca 511 (vocimagene amiretrorepvec) & Toca FC (extended-release flucytosine), initially for the treatment of recurrent high grade glioma, or HGG, a brain cancer with limited treatment options, low survival rates and, therefore, a significant unmet medical need. We are conducting a randomized, controlled Phase 3 clinical trial of Toca 511 & Toca FC in patients with recurrent HGG (Toca 5), which is designed to serve as a registrational trial. Enrollment was completed for this clinical trial in September 2018. In February 2017, the U.S. Food and Drug Administration, or FDA, granted Toca 511 & Toca FC Breakthrough Therapy Designation for the treatment of patients with recurrent HGG and in June 2017 the European Medicines Agency, or EMA, granted Toca 511 Priority Medicines, or PRIME, Designation for the treatment of patients with HGG. Breakthrough Therapy Designation indicates that preliminary clinical evidence demonstrates the drug may have substantial improvement on one or more clinically significant endpoints over available therapy. PRIME Designation indicates that there is a potential to benefit patients with unmet medical needs based on early clinical data. We also have Fast Track Designation (which may lead to priority review of new products that treat serious diseases or conditions and demonstrate the potential to address an unmet medical need) from the FDA for Toca 511 & Toca FC for the treatment of recurrent HGG. We also received Orphan-Drug Designation from the FDA for the treatment of malignant glioma in addition to glioblastoma mutiforme, or GBM. Orphan-Drug Designation is a designation for a product that is designed to treat a rare disease or condition and which, if the product receives the first FDA approval for that disease or condition, may result in a period of regulatory exclusivity, subject to some exceptions. The Committee for Orphan Medicinal Products of the EMA has designated both flucytosine and vocimagene amiretrorepvec as orphan medicinal products indicated for the treatment of glioma. The EMA provides several benefits to drug developers for developing drugs for orphan diseases.

We have conducted three ascending dose Phase 1 clinical trials involving 127 recurrent HGG patients. In these trials, we investigated three modes of Toca 511 delivery: injection into the cavity wall after surgical resection of the recurred tumor (the "resection injection" trial, n=56), direct intratumoral injection without resection (n=54), and intravenous administration followed, approximately one to two weeks later, by resection with further local vector delivery at the time of resection (n=17). Administration of Toca 511 was followed with cycles of Toca FC. In these trials, we observed potential benefits, including durable objective responses, extended overall survival compared to historical controls and a favorable safety profile. We did not reach a dose-limiting toxicity in these trials.

As of the final analysis in December 2017, of the 56 patients enrolled in the ascending-dose resection injection Phase 1 trial, conducted in 7 medical centers, six of the 53 efficacy evaluable patients had durable complete response (durable response is defined as objective response lasting for at least 24 weeks) and remain in response. In a subset of 23 patients that mirrors the entry criteria, clinical setting and dosing for patients in our Phase 3 clinical trial, 5 (21.7%) of these patients had durable complete response. Based on these Phase 1 clinical trial results, we are conducting a Phase 3 clinical trial which is designed to serve as a potential registrational trial in patients with first or second recurrence of HGG who are planning to undergo resection.

Based on preclinical data, we believe Toca 511 & Toca FC may have therapeutic benefit in multiple other solid tumor cancers. We conducted a Phase 1b clinical trial involving intravenous treatment of advanced cancers. In this trial, Toca 511 was administered by intravenous injection followed by subsequent intratumoral injection. We reported a favorable safety and tolerability for the Toca 511 & Toca FC regimen, confirmed vector deposition following intravenous Toca 511 administration in both immunologically "hot" and "cold" areas of metastatic tumors and peripheral blood monitoring suggests immune modulation consistent with observations in our recurring HGG studies. We plan to continue to evaluate safety, vector deposition and immune modulation over time. Data from this trial is informing our future development plans for Toca 511 & Toca FC in patients with solid tumors.

Based on our findings in preclinical studies and clinical trials to date, we believe Toca 511 & Toca FC is a promising candidate for use in newly diagnosed HGG patients in combination with surgery, radiation and chemotherapy. We have partnered with NRG Oncology, a member of the National Cancer Institute's, or NCI, National Clinical Trial Network to develop a clinical trial utilizing Toca 511 & Toca FC for the treatment of patients with newly diagnosed glioblastoma. The proposed Phase 2/3study (NRG-BN006) is expected to begin by the end of 2019 and will be conducted by NRG Oncology under its NCI-funded grant, with us supplying investigational drug and supplemental financial support.

Cancer is the second leading cause of mortality in the United States and accounts for nearly one in four deaths. Early cancer treatments relied on relatively non-specific and highly toxic small molecule chemotherapies. Over the last 20 years, a new paradigm of cancer research and treatment has emerged that is focused on more targeted therapies. Most recently this has included the emergence of immunotherapies that can stimulate a patient's immune system to slow the growth and the spread of, and ideally, eliminate, cancer cells. These therapies have shown the potential to provide dramatic efficacy and to extend survival for cancer patients even in cases in which conventional therapies, such as surgery, chemotherapy and radiotherapy, have already been used.

Despite these advancements, many current immunotherapies, such as checkpoint inhibitors, chimeric antigen receptor, or CAR, and T cell receptor, or TCR, T cells, are limited by their autoimmune and other side effects. Combination treatments are common in cancer, but combinations of immune mediated treatments with systemic cytotoxic chemotherapy may be challenging as chemotherapy is often damaging to the immune system. Thus, immunotherapies effective enough to be able to displace systemic chemotherapy are needed. The utility of oncolytic viruses alone as immunotherapy has been challenged by lack of specificity to tumor cells, injury to healthy tissues, lack of targeting to specific brakes on the immune system, and short-term effect due to effective clearance of the virus. Consequently, there remains a significant need for immunotherapies that are effective as well as safe and tolerable.

In contrast to current immunotherapies, we believe our non-lytic RRV platform and lead product candidate have the potential to selectively infect cancer cells to stimulate robust and durable anti-cancer immune responses with minimal toxicity. Our RRVs are designed to selectively integrate into the DNA of cancer cells which then serve as factories to produce more of these RRVs by budding. The progeny RRV infect neighboring cancer cells, providing long-term presence of the therapeutic gene or genes delivered. Our novel therapies are also designed to break immune tolerance selectively in the tumor microenvironment.

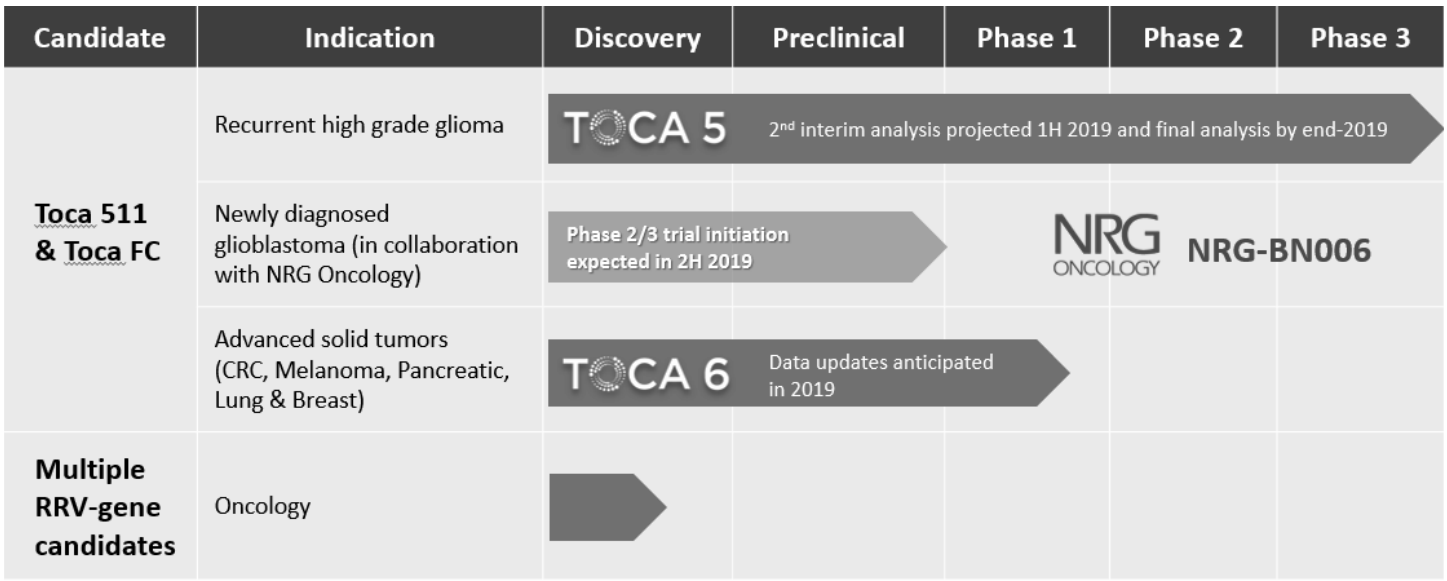
Our RRV platform is versatile and we believe it has the potential to deliver a wide variety of genes selectively to cancer cells. Our first RRV-based immunotherapy product candidate, Toca 511 & Toca FC, is designed to replicate and spread through tumors without cell lysis then, upon activation, directly kill tumor and immune suppressive myeloid cells activating the immune system selectively against cancer through a combination of mechanisms. In addition, we are developing other RRVs to selectively deliver genes to cancer cells against validated immunotherapy targets.

Our Proprietary Technology Platform: Harnessing Cancer Immunotherapy and Gene Therapy Together to Fight Cancer

We believe our investigational gene therapy platform and therapeutic genes represent innovative and differentiated approaches in cancer-selective immunotherapy which have the potential to drive a safe, powerful and durable immune response against cancer, without triggering autoimmunity. We chose to utilize RRVs as the basis of our gene therapy platform for cancer-selective immunotherapy because they exhibit several characteristics that we believe allow us to optimize the safety, delivery and persistence of our therapeutic genes in cancer cells. These characteristics include that they:

- replicate readily and persist in the immune-defective environment of cancer;
- are controlled in healthy tissue by normal immune mechanisms;
- only infect dividing cells such as cancer cells;
- bud from, rather than lyse, infected cancer cells, reducing anti-RRV immune activation;
- infect most cancer types; and
- can cross the blood tumor barrier.

Our Pipeline



Our Strategy

Our focus is to develop and commercialize first-in-class cancer-selective immunotherapies using our proprietary gene therapy platform. Key elements of our strategy include:

- **Advancing Toca 511 & Toca FC rapidly through clinical development and regulatory approval in recurrent HGG**. We are conducting a Phase 3 clinical trial of Toca 511 & Toca FC in patients with recurrent HGG. If we achieve our primary endpoint, overall survival, and/or secondary endpoints, such as durable response rate, we plan to discuss submission of a biologics license application, or BLA, based on this data with the FDA. We believe such data could serve as the basis for regulatory approval. In February 2017, the FDA granted Toca 511 & Toca FC Breakthrough Therapy Designation for the treatment of patients with recurrent HGG and in June 2017 the EMA granted Toca 511 PRIME Designation for the treatment of patients with HGG. In October 2017, following discussions with the FDA, we redesigned our Phase 2/3 clinical trial to be a single Phase 3 clinical trial, thereby including the 187 patients that were previously enrolled in the Phase 2/3 clinical trial in the total of 380 patients expected to enroll in the redesigned trial. The primary endpoint of the redesigned trial is OS. The primary endpoint assumes a median OS of 9.8 months for the control arm versus 14.3 months for the Toca 511 & Toca FC arm. A total of 257 events will provide the redesigned trial with 85% power to detect a hazard ratio of 0.685. The redesigned trial includes planned interim analyses at 50% and 75% of total events. The Independent Data Monitoring Committee completed its review at 50% of total events and recommended the Phase 3 clinical trial should continue as planned without modification. We plan to conduct the second interim analysis in the second quarter of 2019 after 75% of total events have occurred and the final analysis in the fourth quarter of 2019 after 100% of total events have occurred.
- **Expanding the therapeutic use of Toca 511 & Toca FC into newly diagnosed HGG and other solid cancer indications**. We have partnered with NRG Oncology to develop a clinical trial utilizing Toca 511 & Toca FC for the treatment of patients with newly diagnosed glioblastoma. The proposed Phase 2/3 study (NRG-BN006) is expected to begin by the end of 2019 and will be conducted by NRG Oncology under its NCI-funded grant, with us supplying investigational drug and supplemental financial support. We believe Toca 511 & Toca FC has potential broad applicability in the treatment of solid cancers. In July 2016, we initiated a Phase 1b clinical trial involving intravenous treatment of advanced cancers. In this trial we reported a favorable safety and tolerability for the Toca 511 & Toca FC regimen, confirmed vector deposition following intravenous Toca 511 administration in both immunologically "hot" and "cold" areas of metastatic tumors and peripheral blood monitoring suggests immune modulation consistent with observations in our recurring HGG studies. These data are helping to inform our future development plans for Toca 511 & Toca FC in patients with advanced cancers.
- **Commercializing Toca 511 & Toca FC in the United States**. If approved, we plan to build the capabilities to commercialize Toca 511 & Toca FC through medical science liaisons and a specialty sales force in the United States.
- **Pursuing strategic partnerships to expand the commercial opportunity for, and accelerate the development of, our product candidates**. In April 2018 we entered into a license agreement with Beijing Apollo Venus Biomedical Technology Limited, and ApolloBio Corp., collectively ApolloBio, pursuant to which we granted to ApolloBio an exclusive license to develop and commercialize Toca 511 & Toca FC within the greater China region, including mainland

China, Hong Kong, Macao and Taiwan. We may choose to further partner our lead product candidate or our future product candidates in key markets or therapeutic areas where a partner could bring additional resources and expertise.

- **Leveraging our RRV platform and core competencies to continue discovering and developing a broad pipeline of novel cancer-selective immunotherapies**. We believe there is a significant opportunity to develop additional immunotherapy product candidates utilizing our RRV platform. Our scientists have broad expertise in the field of gene therapy, spanning discovery, development and manufacturing. We intend to leverage our platform and expertise to discover and develop a broad pipeline of cancer-selective immunotherapies to help patients fight their cancers without the severe side effect profile typical of cancer treatments.

Our Approach to Immunotherapy

Due to the novel mechanisms of action and favorable safety profile in clinical studies to date, we believe our RRVs represent an important advancement in the field of immunotherapy. Our approach is designed to enhance immune responses against cancer cells and, in the case of our lead product candidate, Toca 511 & Toca FC, reduce immune-suppressive myeloid cell inhibition of the immune system. Also, we believe our RRV platform has the potential to be safely combined with conventional therapies and complement emerging checkpoint inhibitors and other approaches to cancer immunotherapy.

Resection Injection Trial

As of the final analysis in December 2017, of the 56 patients enrolled in the ascending-dose resection injection Phase 1 trial, conducted in 7 medical centers, six of the 53 efficacy evaluable patients had durable complete response (durable response is defined as objective response lasting for at least 24 weeks) and remained in response. Responses were assessed by independent radiology review of magnetic resonance imaging, or MRI, brain scans. In a subset of 23 patients that mirrors the entry criteria, clinical setting and dosing for patients in our Phase 3 clinical trial, 5 (21.7%) of these patients had a durable complete response. In addition:

- Median duration of response had not been reached after a median follow up of 37.4 months (range: 14.1 to 44.9 months).
- Stable disease (lasting at least eight weeks) was observed in five additional patients, bringing the clinical benefit rate to 43.5% (10/23 patients).
- Landmark overall survival, or OS, rates at two and three years (OS24, OS36) was 34.8% and 26.1%, respectively.

Resection Study: All Responses are in the Higher Dose Cohort

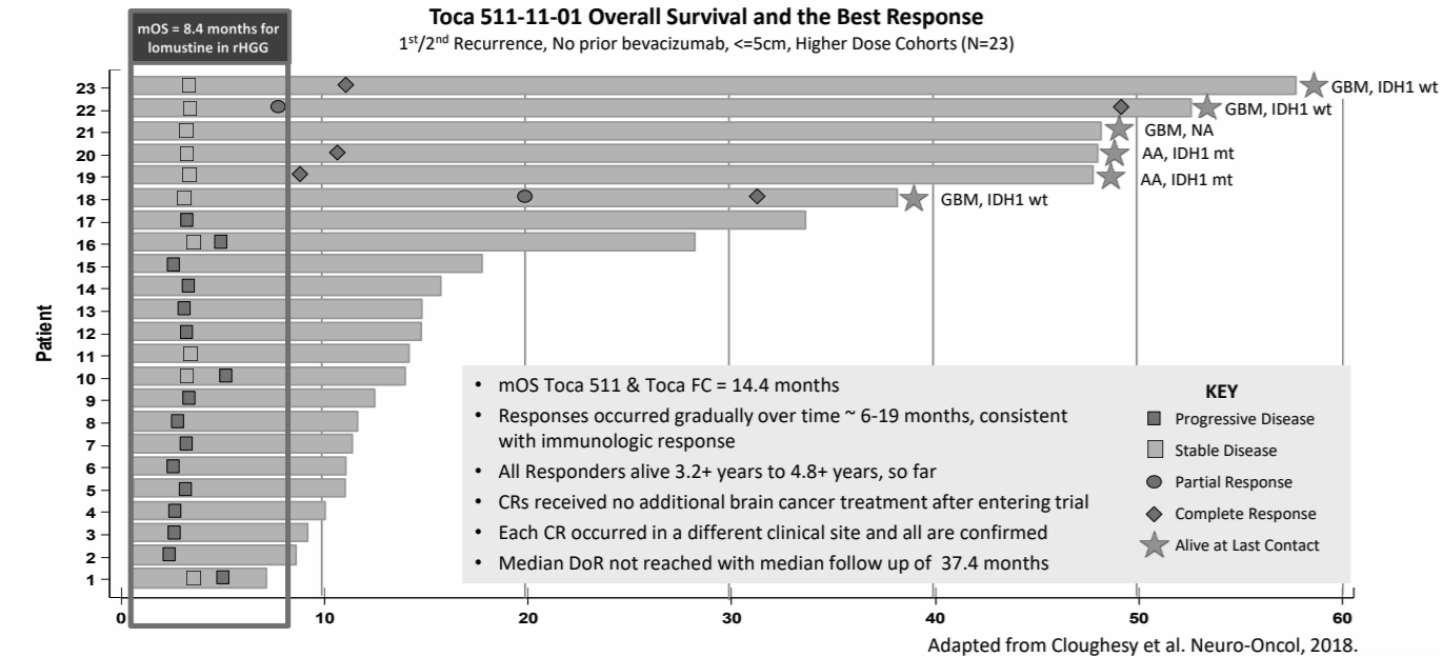
Response Category[1]	All Patients N=53 n (%)	Higher Doses & Phase 3 Entry Criteria Subset N=23 n (%)[2]
Overall response	**6CR (11.3)**	**5CR (21.7)**
Stable disease (SD)	12 (22.6)	5 (21.7)
Progressive disease	35 (66.0)	13 (56.5)
Clinical Benefit Rate (CR, PR, and SD at 6 wks)	16 (30.2)	10 (43.5)

1 Includes MRI by independent radiology review and clinical data; patients categorized by best response achieved during MRI screenings.

2 Higher doses (cohorts 4-7a) and meet Phase 3 entry criteria of 1 st and 2 nd recurrence, no prior Avastin in rHGG, tumor not > 5cm

In the table below, as of the final analysis in December 2017, clinical data for each of the 23 patients is represented by a blue bar, with the x-axis measuring months of survival. Change in patient tumor status (i.e., PD, SD, PR, or CR) are represented along the bar, with the status at the end representing “best response” during the treatment. The green stars indicate the six patients who remain alive at the latest data cutoff. The responses, which occur approximately six to 19 months after Toca 511 administration, are consistent with immunologic response and all responders who remain alive have received no therapy other than Toca 511 & Toca FC since enrolling in the trial. Median duration of response had not been reached after a median follow up of 37.4 months (range 14.1 to 44.9 months).

Resection Study: Long-Term Survival in Higher Dose Cohort



Historical estimate for mOS for lomustine is based on weighted average (Batchelor 2013, Taal 2014, Wick 2010, EORTC 26101: n=352).

Furthermore, an independent radiology review of MRI brain scans from our Phase 1 clinical trials identified tumor shrinkage in some patients, including several CRs. All patients in the resection injection trial with objective responses remain with durable response as of December 2017, for a median of 37.4 months, which represents approximately four times longer duration of response relative to responses from a clinical trial of lomustine which showed an estimated median duration of response of approximately six months (range of response duration was 2.79 to 9.62 months).

	Lomustine[1]	Toca 511 & Toca FC[2]
Overall response rate CRs & PRs	4.3%	21.7%
Duration of response (months)	~6.2	>37.4 (median not reached)
Median Survival (months)	7.1	14.4

1 Adapted from Wick, JCO 2010.

2 Higher doses (cohorts 4-7a) and 1st and 2nd recurrence, no prior Avastin in rHGG, tumor not > 5cm.

Based on these data as well as a favorable safety profile we initiated a registration-directed Toca 5 clinical trial of Toca 511 & Toca FC in this same setting, enrolling patients with recurrent HGG who were planning for further resection of their tumor. Also, we chose the resection setting for the Toca 5 clinical trial because we believe that resection of the bulk of the tumor and then injection into the residual tumor left behind in the cavity wall provides a longer opportunity for the treatment to activate the immune system against the growing tumor.

We also tested for changes in CD4 and CD8 T cells in blood during the study, allowing us to evaluate both the safety and activity of our treatment on the immune system. Changes were observed in these preliminary tests that are consistent with an increased T cell activation during therapy in patients with stable disease or complete responses.

Biomarkers

As part of our exploration of mutation profiles that may serve as a biomarker for patients with a higher likelihood of long-term benefit, we observed that objective responses occurred in patients with IDH1 mutant (mt) and IDH1 wild type (wt) tumors. Approximately 15% of the population with HGG is believed to have the IDH1 mutation. Across the Phase 1 clinical trial program, and as of December 2017, the three patients with known IDH1 mutations at first recurrence had CRs (two in the resection injection study and one patient in the intravenous study with a radiologic CR) and all these IDH1 mutation patients are alive (range of survival 12.2 to 35.3 months), suggesting a potential association of IDH1 mutation to survival.

Pooled Safety Data

Toca 511 & Toca FC has been well tolerated in clinical trials to date. There has been little difference in adverse events among the three Phase 1 clinical trials in recurrent HGG. For this reason we chose to pool safety data across the three ascending Phase 1 clinical trials. As shown in the table below, in 127 patients who received Toca 511, treatment-related adverse events were reported in 57.5% of the patients; Grade 3/4 treatment-related adverse events were reported in 8.7% of patients. Grade 3/4 treatment-related serious adverse events were reported in 6.3% of patients treated with Toca 511; Grade 3/4 treatment-related serious adverse event of vasogenic cerebral edema was reported in 1.6% of patient; both events were Grade 3. We monitored blood samples for viral RNA and DNA and found that quantitative levels were cleared within two weeks to four months of administration. Also, we analyzed tumor and blood samples for viral insertion sites and demonstrated an absence of clonality, supporting viral safety. We also monitor Toca FC blood levels for the first treatment cycle and whenever the dose is increased. This helps us to adjust dosing upwards in patients with Toca FC blood levels below the target range. The favorable toxicity profile of Toca 511 & Toca FC suggests that combination with other modalities such as chemotherapy or radiation should yield little incremental toxicity.

Adverse Events Related to Toca 511 & Toca FC – Pooled Across Studies

Low Incidence of Grade 3/4 Treatment-Related AEs

Treatment-Related AEs	Toca 511 & Toca FC N=127	
	Grade 1/2	Grade 3/4
	n (%)	n (%)
Any treatment-related event	**62 (48.8)**	**11 (8.7)**
Treatment-related event ≥5% patients		
Fatigue	37 (29.1)	1 (<1)
Diarrhea	17 (13.3)	1 (<1)
Nausea	14 (11.0)	0
Headache	8 (6.2)	1 (<1)
Decreased appetite	7 (5.5)	0

Low Incidence of Treatment-Related SAEs

Treatment-Related SAEs	Toca 511 & Toca FC N=127	
	Grade 1/2	Grade 3/4
	n (%)	n (%)
Any treatment-related event	1 (<1)	8 (6.3)
Treatment-related event ≥1% patients		
Vasogenic cerebral oedema[1]	0	2 (1.6)

[1] Both SAEs were Grade 3; no Grade 4 SAE

Ongoing Phase 3 Clinical Trial

In November 2015, we initiated the Phase 2 portion of a randomized, controlled Phase 2/3 clinical trial of Toca 511 & Toca FC against the current standard of care in recurrent HGG. In this clinical trial we are using doses of Toca 511 & Toca FC of 4 mL and 220 mg/kg/day, respectively, equivalent to the doses used in the Higher Dose Cohort of our Phase 1 resection injection trial. Enrollment criteria for patients in this clinical trial includes first or second recurrence of HGG, no prior treatment with bevacizumab for recurrent HGG, and a tumor size of less than or equal to five centimeters.

In October 2017, based on our communications with the FDA under Breakthrough Therapy Designation, we modified the original two-step trial design (Phase 2 followed by Phase 3) into a seamless, Phase 3 pivotal trial, also known as the Toca 5 trial. Enrollment of the planned 380 patients in the Toca 5 trial was completed in September 2018. The redesigned trial includes planned interim analyses at 50% and 75% of total events. The Independent Data Monitoring Committee completed its review at 50% of total events and recommended the Phase 3 clinical trial should continue as planned without modification. We plan to conduct the second interim analysis in the second quarter of 2019 after 75% of total events have occurred and the final analysis in the fourth quarter of 2019 after 100% of total events have occurred.

Phase 1b Solid Tumor Clinical Trial

We conducted a Phase 1b clinical trial involving intravenous treatment of advanced cancers. In this trial, Toca 511 was administered by intravenous injection followed by intratumoral injection. We reported a favorable safety and tolerability for the Toca 511 & Toca FC regimen, confirmed vector deposition following intravenous Toca 511 administration in both immunologically "hot" and "cold" areas of metastatic tumors and peripheral blood monitoring suggests immune modulation consistent with observations in our recurring HGG studies. We plan to continue to evaluate safety, vector deposition and immune modulation over time. Data from this trial are informing our future development plans for Toca 511 & Toca FC in patients with solid tumors.

Planned Clinical Trials

In 2019, we plan to advance our clinical development evaluating Toca 511 & Toca FC in patients with newly diagnosed HGG. The proposed Phase 2/3 trial (NRG-BN006) is expected to begin by the end of 2019 and will be conducted by NRG Oncology. The primary goals of this study will be to evaluate the safety and preliminary efficacy of Toca 511 delivered at the time of resection and Toca FC subsequently delivered in conjunction with radiation and temozolomide.

Preclinical Studies of Toca 511 & 5-FC

We believe our preclinical studies support the clinical development of Toca 511 & Toca FC in brain cancers and other cancers both as a stand-alone regimen and in combination with current treatments. During preclinical testing of Toca 511 we observed that treatment with Toca 511 & 5-FC had two powerful mechanisms of action: direct killing of cancer cells and activation of the immune system against the cancer cells. 5-FC, which we use in our preclinical studies, is the active component of the Toca FC tablets we use in humans.

Discovery

We believe there is a significant opportunity to develop additional immunotherapy product candidates utilizing our RRV platform. We intend to leverage our technology platform and expertise to discover a broad pipeline of cancer-selective immunotherapies.

Manufacturing

Our lead product candidate, Toca 511 & Toca FC, consists of a biological component and a drug component, which are separately manufactured and are both covered by our proprietary intellectual property. The process for Toca 511 manufacturing and testing has been developed internally and we believe that the process itself and the expertise to design and implement this process as well as the testing are significant assets. The process and the vector composition are covered by patents, patent applications and trade secrets. The process for Toca FC (extended release 5-FC) was also designed internally. We rely on third-party contract manufacturing organizations, or CMOs, for both of these manufacturing processes to produce our final product for clinical use, as currently we do not own or operate manufacturing facilities. In addition we utilize contract testing organizations, or CTOs, for the establishment and performance of validated product release assays for Toca 511 & Toca FC material. For Toca FC and Toca 511, we require that our CMOs produce bulk drug substances and finished drug products compliant with current Good Manufacturing Practices, or cGMP, requirements and all other applicable laws and regulations. We plan to release material with appropriately qualified assays by our CTOs, who we require to operate under cGMP. We will retain final responsibility for product release and maintain an appropriate quality assurance capability to meet this need. We will continue to rely on CMOs and CTOs to manufacture and perform release testing, respectively, of our products for commercial sale. We maintain agreements with manufacturers and testing laboratories that include confidentiality and intellectual property provisions to protect our proprietary rights related to our product candidates and testing methods.

We use a producer cell line to create Toca 511 and currently rely on a limited number of CMOs to manufacture Toca 511. We believe that our current manufacturing capacity for Toca 511 will be sufficient to support our ongoing and planned clinical trials and commercial manufacturing needs.

Manufacturing for Toca FC generally encompasses both the chemical synthesis of the active pharmaceutical ingredient, or API, and its formulation and fill/finish of the final product. We currently utilize a limited number of CMOs for the production of the API and the final drug product tablets. We believe we have the manufacturing capacity to supply the drug product tablets for our ongoing and planned clinical trials and commercial supply.

We currently have no plans to build our own manufacturing capacity to manufacture Toca 511 or Toca FC.

License and Collaboration Agreements

License Agreement with ApolloBio

In April 2018, we entered into a license agreement with ApolloBio, or the ApolloBio License Agreement, which became effective in July 2018, pursuant to which we granted ApolloBio an exclusive license to develop and commercialize Toca 511 & Toca FC within the greater China region, including mainland China, Hong Kong, Macao and Taiwan, or the Licensed Territory.

Under the ApolloBio License Agreement, in addition to an aggregate upfront payment of $16.0 million, we are eligible to receive up to an aggregate $111.0 million, less withholding and other taxes, upon the achievement of specified development and commercial milestones. We are also eligible for low double-digit tiered royalty payments based on annual net sales of licensed products in the Licensed Territory, subject to reduction under specified circumstances. ApolloBio will be responsible for all development and commercialization costs in the Licensed Territory. Future payments by ApolloBio are subject to the People's Republic of China, or PRC currency exchange approval and may be subject to other approvals by PRC authorities.

Under the ApolloBio License Agreement, we have received net proceeds of $15.2 million which was comprised of a $16.0 million up-front payment and a $2.0 million milestone payment less $1.7 million in foreign income taxes and $1.1 million in certain foreign non-income taxes.

Unless earlier terminated, the ApolloBio License Agreement will expire upon the expiration of the last-to-expire royalty term for any and all licensed products, which royalty term is, with respect to a licensed product in a particular region (*i.e.*, mainland China, Hong Kong, Macao and Taiwan) of the Licensed Territory, or each, a Region, the latest of (i) 10 years after the first commercial sale of such licensed product in such Region, (ii) the expiration of all regulatory exclusivity as to such licensed product in such Region and (iii) the date of expiration of the last valid patent claim covering such licensed product in such Region. Either party may terminate the ApolloBio License Agreement upon a material breach by the other party that remains uncured following 60 days (or, with respect to any payment breach, 10 days) after the date of written notice of such breach. ApolloBio may terminate the ApolloBio License Agreement at any time by providing 90 days' prior written notice to us. In addition, we may terminate the ApolloBio License Agreement upon written notice to ApolloBio under specified circumstances if ApolloBio challenges the licensed patent rights.

Laboratory Services and License Agreement with Siemens

In November 2011, we entered into a laboratory services and license agreement with Siemens Healthcare Diagnostics Inc., or Siemens, which we amended in June 2015, pursuant to which we agreed to engage Siemens (i) to develop and perform certain *in vitro* diagnostic assays in connection with the cancer therapy trials of Toca 511 & Toca FC, (ii) concurrently and/or thereafter, to further develop, obtain FDA approval for, and perform one or more of such *in vitro* diagnostic assays as drug monitoring diagnostics for Toca 511 & Toca FC as Toca 511 & Toca FC receives marketing approval from the FDA, and (iii) following FDA approval of such *in vitro* diagnostic assay as a monitoring diagnostic, to perform such *in vitro* diagnostic monitoring assays as necessary in connection with post-marketing clinical trials of Toca 511 & Toca FC and, if appropriate, as commercial diagnostic tests. We granted Siemens the licensed intellectual property covered by the agreement on an exclusive and non-exclusive basis, depending on Siemens' use of such intellectual property.

Under the terms of the agreement, Siemens paid us an initial upfront payment of $0.5 million. Additionally, beginning with the first commercial sale of a product that has received approval for clinical use under the agreement, Siemens will pay us a royalty in the 10-20 percent range of net assay revenue with respect to approved designated assay products and net sales revenue with respect to approved *in vitro* diagnostic products, until the fifth anniversary of such commercial sale, subject to certain reductions. Beginning with the first commercial sale of Toca 511 or Toca FC, we will pay a royalty to Siemens in the low single-digit percentage range on net product sales of Toca 511 & Toca FC for sales up to the mid-nine-digit dollar range per year, until the fifth anniversary of such commercial sale.

The term of this agreement will continue until the expiration of all payment obligations. The agreement provides that it may be terminated by either party upon written notice to the other party in the event of the other party's material breach of the agreement if such breach remains uncured for 45 days, or in the event the other party files a voluntary petition in bankruptcy, is adjudicated as bankrupt or insolvent after all appeals are exhausted, makes a general assignment for the benefit of creditors or fails to discharge or have dismissed within 60 days an involuntary petition in bankruptcy filed against it. If market approval is rejected by the FDA, Siemens must provide us with prompt written notice. Should the parties be unable to reach mutual agreement regarding regulatory strategy within 20 business days of such notice, then either party may terminate the agreement upon written notice to the other party. Siemens may terminate the agreement for any reason upon 90 days prior written notice to us, provided that, notwithstanding such termination, Siemens must continue to provide the laboratory services for any of our trials the protocol for which has been submitted to FDA until the conclusion of such pre-approval trial. Siemens may also terminate the agreement if, after using commercially reasonable efforts, certain assay specifications are not achieved. If Siemens terminates the agreement for breach of contract by us, the licenses granted to Siemens will survive such termination and will become non-exclusive, perpetual and irrevocable, provided that Siemens will have the right to terminate any such license at any time upon written notice to us. If the agreement expires, or if the

agreement is terminated by us for breach of contract by Siemens or for failure to reach an agreement on regulatory strategy, the restriction in the license granted to activities outside of the territory will terminate, and we will have the right to pursue development and commercialization of companion diagnostics for products with one or more other partners in the territory, and to grant to such other partners sublicenses of our rights under the agreement. If the agreement is terminated by either party for failure to reach an agreement on regulatory strategy, or by Siemens by 90 days written notice, for a minimum of 45 days after the later of (i) the termination date or (ii) completion of any required post-termination laboratory services and delivery to us of all results thereof, Siemens must retain any stocks of qualified reagents for the assays that remain as of Siemens' completion of such laboratory services, and, upon our request made at any time during such 45-day period, Siemens must deliver such remaining stocks to us, provided that we shall have executed documentation reasonably satisfactory to Siemens acknowledging that the use of such reagents is restricted to investigational use pursuant to our investigational new drug application, or IND, and any other use permitted by, and in compliance with, applicable laws, regulatory guidelines and regulatory approvals.

License Agreement with USC

In October 2007, we entered into a license agreement with the University of Southern California, or USC, pursuant to which we received a worldwide, exclusive license to, among other things, manufacture and market products utilizing inventions related to our RRV platform and other key technology.

Under the terms of the agreement, we paid an initial license fee to USC in the low six-digit dollar range and issued to USC shares of our common stock in an amount equal to the low single-digit percent range of all the number of shares of common stock issued at the time shares were issued to our six founders prior to the date of the agreement. Pursuant to the agreement, we owe USC a royalty in the low single-digit percent range of our and our sub-licensee's net sales of products covered by the agreement. In addition, we owe USC an additional royalty in the low single-digit percent range of revenue from our sub-licensees. Once our and our sub-licensees net sales reach an amount in the mid-seven digit dollar range, the minimum annual royalty payment due to USC will be in the low six-digit dollar range. Our royalty obligations continue on a licensed product-by-licensed product and country-by-country basis until the expiration of the last valid claim in the licensed patent covering a licensed product in such country.

The term of this agreement will continue until all of our royalty payment obligations have expired unless terminated earlier. The agreement provides that it may be terminated by either party upon written notice to the other party in the event of the other party's material breach of the agreement if such breach remains uncured for 45 days. We may terminate the agreement without cause upon 45 days' advance written notice to USC. USC may also terminate the agreement upon notice to us upon (i) the declaration by a court of competent jurisdiction that we are bankrupt and our assets are to be liquidated pursuant to the U.S. Bankruptcy Code; (ii) upon the filing or institution by us of bankruptcy, liquidation or receivership proceedings under Chapter 7 of the U.S. Bankruptcy Code; (iii) upon an assignment of a substantial portion of our assets for the benefit of creditors; or (iv) in the event a receiver or custodian is appointed in bankruptcy for all or substantially all of our business; provided, however, that in the case of any involuntary proceeding, such right to terminate shall only become effective if the proceeding is not dismissed within 120 days after the filing thereof. Upon termination of the agreement, all rights granted to or provided by each party to the other shall automatically and irrevocably revert to the granting party.

Grants

In August 2017, we were awarded a $2.0 million grant by the U.S. Food and Drug Administration Office of Orphan Products Development to support our Phase 3 clinical trial, or OOPD Grant. Under the grant agreement, we will be reimbursed for qualifying expenses over a four-year period subject to the availability of funds and satisfactory progress of the trial. At December 31, 2018, we had received $1.0 million relating to the OOPD Grant.

We have also received grants from the following entities: National Institutes of Health, Voices Against Brain Cancer, Musella Foundation, Accelerate Brain Cancer Cure, Inc., National Brain Tumor Society, American Brain Tumor Association, Adenoid Cystic Carcinoma Research Foundation, and Internal Revenue Service — Qualifying Therapeutic Discovery Project Program.

Sales and Marketing

We plan to build at the appropriate time a commercial infrastructure targeting oncologists, neuro-oncologists and neurosurgeons and related clinicians and health care workers in leading and regional cancer centers in the United States.

We anticipate that our commercial infrastructure will be built around a "high-touch" model to maximize patient access to our products. In addition to an internal team of dedicated medical sales, marketing, medical affairs, reimbursement, and commercial operations personnel we anticipate leveraging external capabilities such as contract pharmacy services. It is possible that a Risk Evaluation Mitigation Strategy program, or REMS, will be required for our products.

For our lead product candidate, Toca 511 & Toca FC for HGG, we have established a base of scientific familiarity with leading physicians in the United States, EU, Canada, South Korea, Israel and Japan. If we obtain regulatory approval, we expect that the base of familiarity we have built with leading international brain cancer centers during the conduct of our clinical trials, including the Toca 5 trial, will help drive market acceptance of our product. We believe that the majority of patients undergoing treatment for HGG in the United States are treated at approximately 60 brain cancer centers in the United States, many of which have participated in our clinical trials. Therefore, we believe a highly specialized, relatively small, medically-focused sales force, in addition to medical science liasons, will be sufficient to support the commercialization of our product.

Outside the United States, we may build our own commercial infrastructure or consider opportunities to enter into out-licensing or co-promotion agreements with other pharmaceutical or biotechnology companies to develop and/or commercialize our product candidates outside the United States. In April 2018, we entered into the ApolloBio License Agreement with ApolloBio pursuant to which we granted ApolloBio an exclusive license to develop and commercialize Toca 511 & Toca FC within the greater China region, including mainland China, Hong Kong, Macao and Taiwan.

We currently have limited sales and marketing or distribution capabilities or in-house personnel specializing in these functions.

Intellectual Property

Intellectual property is of vital importance in our field and in biotechnology generally. We seek to protect and enhance proprietary technology, inventions, and improvements that are commercially important to the development of our business by seeking, maintaining, and defending patent rights, whether developed internally or licensed from third parties.

We will also seek to rely on regulatory protection afforded through Orphan-Drug Designations, data exclusivity, market exclusivity and patent term extensions where available.

We have obtained Orphan-Drug Designation for Toca 511 & Toca FC for the treatment of malignant glioma in addition to GBM, which makes the product eligible for a period of orphan drug exclusivity, if approved in this indication, under certain conditions. We believe that approval under a biologics license application, or BLA, will be eligible for 12 years of market exclusivity in the United States, 10 years of market exclusivity in Europe and significant durations in other markets, which would be complementary to any relevant patent exclusivity.

Through licensing and developing our own portfolio, and as of December 31, 2018, we have rights to 14 issued patents in the United States, eight of which are assigned to us and six of which are exclusively licensed to us, and 81 issued and granted patents in foreign countries, 62 of which are assigned to us and 19 of which are exclusively licensed to us, 12 patent applications in the United States, all of which are assigned to us and 64 patent applications in foreign countries, all of which are assigned to us. We believe that the issued patents will provide coverage on our technology platform and product candidates until approximately 2030. We file intellectual property we believe to be key to our business at a minimum in jurisdictions including the United States, Europe and Japan. Our original core technology was licensed from USC and The Regents of the University of California. Families within the portfolio are directed to our RRV technology platform, the modified CD gene that we use in Toca 511, various other therapeutic modalities and genes for use with RRV, manufacturing methods for RRV, the extended release Toca FC formulation, various combination therapies with Toca 511 & Toca FC and other agents, intravenous administration of RRV and diagnostic assays for detection of RRV.

We possess significant knowledge relating to the construction, manufacture, development and protection of gene therapy products. We aim to protect certain intellectual property through a trade secret strategy.

Competition

The biotechnology and pharmaceutical industries, and the immunotherapy subsector, are characterized by rapid evolution of technologies, fierce competition and strong defense of intellectual property. A wide variety of institutions, including large pharmaceutical companies, specialty biotechnology companies, academic research departments and public and private research institutions are actively developing potentially competitive products and technologies. We face substantial competition from biotechnology and pharmaceutical companies developing products in immunotherapy and in our lead indication.

Companies developing other immunotherapy products generally fall within the following categories:

- diversified pharmaceutical companies developing immunotherapies, including checkpoint inhibitors;
- companies aimed at stimulating immune responses;
- companies developing CAR and TCR T cells; and
- companies developing virus-based technology.

Any product candidates that we successfully develop and commercialize may compete with existing and new therapies that may become available in the future. The availability of coverage and adequate reimbursement from government and other third-party payers will also significantly affect the pricing and competitiveness of our products.

Many of our competitors, either alone or with strategic partners, have substantially greater financial, technical and human resources than we do. Accordingly, our competitors may be more successful than we are in obtaining approval for treatments and achieving widespread market acceptance, rendering our treatments obsolete or non-competitive. Accelerated mergers and acquisitions activity in the biotechnology and pharmaceutical industries may result in even more resources being concentrated among a smaller number of our competitors. These companies also compete with us in recruiting and retaining qualified scientific and management personnel, establishing clinical trial sites and patient registration for clinical trials and acquiring technologies complementary to, or necessary for, our programs. Smaller or early-stage companies may also prove to be significant competitors, particularly through collaborative arrangements with large and established companies.

Our commercial opportunity could be substantially limited in the event that our competitors develop and commercialize products that are more effective, safer, less toxic, more convenient or cheaper than our comparable products. In geographies that are critical to our commercial success, competitors may also obtain regulatory approvals before us, resulting in our competitors building a strong market position in advance of our product's entry. We believe the competitive factors that will determine the success of our programs will be the efficacy, safety, pricing and reimbursement, and convenience of our product candidates.

Government Regulation

Our most advanced product candidate, Toca 511 & Toca FC, is subject to regulation as a combination product in the U.S., which means that it is comprised of both a drug product and a biologic product. If marketed individually, each component would be subject to different regulatory pathways and reviewed by different Centers within the FDA. A combination product, however, is assigned to a Center that will have primary jurisdiction over its regulation based on a determination of the combination product's primary mode of action, which is the single mode of action that provides the most important therapeutic action. In the case of our Toca 511 & Toca FC product candidate, we believe that the primary mode of action is attributable to the biologic component of the product, which means that the Food and Drug Administration's Center for Biologics Evaluation and Research, or CBER, has primary jurisdiction over premarket development. We have had formal communication with the Center for Drug Evaluation and Research, or CDER, acknowledging that CBER will be the lead review agency while CDER will be a consulting agency for the Toca FC product component. Accordingly, we are investigating Toca 511 & Toca FC pursuant to a single IND and we plan to seek approval of the combination product through a single BLA. Based on our discussions with the FDA to date, we do not anticipate that the FDA will require a separate marketing authorization for Toca FC, the small molecule drug component of the combination.

Combination products comprised of biological products, such as gene therapy products, and small molecule drugs, are subject to regulation under the Federal Food, Drug, and Cosmetic Act, or FD&C Act, and the Public Health Service Act, or PHS Act, and other federal, state, local, and foreign statutes and regulations. Both the FD&C Act and the PHS Act and their corresponding regulations govern, among other things, the testing, manufacturing, safety, efficacy, labeling, packaging, storage, record keeping, distribution, reporting, advertising, and other promotional practices involving combination products. In the United States, before clinical testing of such combination products, we must submit an IND to the FDA, which reviews the clinical protocol, and the IND must become effective before clinical studies may begin. FDA approval also must be obtained before marketing of combination products. The process of obtaining regulatory approvals and the subsequent compliance with appropriate federal, state, local, and foreign statutes and regulations require the expenditure of substantial time and financial resources.

Within the FDA, CBER regulates gene therapy products. The FDA has published guidance documents with respect to the development and submission of gene therapy products, including their preclinical assessment, clinical protocols, observing patients involved in gene therapy studies for delayed adverse events, potency testing, and chemistry, manufacturing and control information in gene therapy INDs.

Ethical, social, and legal concerns about gene therapy, genetic testing, and genetic research could result in additional regulations restricting or prohibiting the processes we may use. Federal and state agencies, congressional committees and foreign governments have expressed interest in further regulating biotechnology. More restrictive regulations or claims that our products are unsafe or pose a hazard could prevent us from commercializing any products. New government requirements may be established that could delay or prevent regulatory approval of our product candidates under development. It is impossible to predict whether legislative changes will be enacted, regulations, policies, or guidance changed, or interpretations by agencies or courts changed, or what the impact of such changes, if any, may be.

U.S. Combination Products Development Process

The process required by the FDA before a biological product, including our Toca 511 & Toca FC combination product candidate, may be marketed in the United States generally involves the following:

- completion of nonclinical laboratory tests and animal studies according to good laboratory practices, or GLPs, and applicable requirements for the humane use of laboratory animals or other applicable regulations;
- submission to the FDA of an application for an IND, which must become effective before human clinical trials may begin;
- performance of adequate and well-controlled human clinical trials according to the FDA's regulations commonly referred to as good clinical practices, or GCPs, and any additional requirements for the protection of human research patients and their health information, to establish the safety, purity, and potency of the proposed biological product for its intended use;
- submission to the FDA of a BLA for marketing approval that includes substantive evidence of safety, purity, and potency from results of nonclinical testing and clinical trials;
- satisfactory completion of an FDA inspection of the manufacturing facility or facilities where the components of the combination product are produced and tested to assess compliance with cGMP requirements to assure that the facilities, methods and controls are adequate to preserve the product's identity, strength, quality and purity;
- potential FDA audit of the nonclinical and clinical trial sites that generated the data in support of the BLA; and
- FDA review and approval, or licensure, of the BLA.

Before testing any product candidate, including a gene therapy product, in humans, the product candidate enters the preclinical testing stage. Preclinical tests, also referred to as nonclinical studies, include laboratory evaluations of product chemistry, toxicity and formulation, as well as animal studies to assess the potential safety and activity of the product candidate. The conduct of certain preclinical tests must comply with federal regulations and requirements including GLPs.

Where a gene therapy study is conducted at, or sponsored by, institutions receiving NIH funding for recombinant DNA research, the NIH Guidelines for Research Involving Recombinant DNA Molecules, or NIH Guidelines, are mandatory, however many companies and other institutions not otherwise subject to the NIH Guidelines voluntarily follow them. The NIH is responsible for convening its Recombinant DNA Advisory Committee, a federal advisory committee, which discusses protocols that raise novel or particularly important scientific, safety or ethical considerations. Current NIH guidelines are in flux and NIH has released a proposal to streamline oversight for gene therapy research. However, the roles and responsibilities of institutional biosafety committees, or IBCs at the local level will continue as described in the NIH guidelines.

The clinical trial sponsor must submit the results of the preclinical tests, together with manufacturing information, analytical data, any available clinical data or literature and a proposed clinical protocol, to the FDA as part of the IND. Some preclinical testing may continue even after the IND is submitted. The IND automatically becomes effective 30 days after receipt by the FDA, unless the FDA places the clinical trial on a clinical hold within that 30-day time period. In such a case, the IND sponsor and the FDA must resolve any outstanding concerns before the clinical trial can begin. The FDA may also impose clinical holds on a product candidate at any time before or during clinical trials due to safety concerns or non-compliance. If the FDA imposes a clinical hold, trials may not recommence without FDA authorization and then only under terms authorized by the FDA. Accordingly, we cannot be sure that submission of an IND will result in the FDA allowing clinical trials to begin, or that, once begun, issues will not arise that suspend or terminate such trials.

Clinical trials involve the administration of the product candidate to healthy volunteers or patients under the supervision of qualified investigators, generally physicians not employed by or under the clinical trial sponsor's control. Clinical trials are conducted under protocols detailing, among other things, the objectives of the clinical trial, dosing procedures, patient selection and exclusion criteria, and the parameters to be used to monitor patient safety, including stopping rules that assure a clinical trial will be stopped if certain adverse events should occur. Each protocol and any amendments to the protocol must be submitted to the FDA as part of the IND. Clinical trials must be conducted and monitored in accordance with the FDA's regulations comprising the GCP requirements, including the requirement that all patients provide informed consent. Further, each clinical trial must be reviewed and approved by an independent institutional review board, or IRB, at or servicing each institution at which the clinical trial will be conducted. An IRB is charged with protecting the welfare and rights of clinical trial participants and considers such items as whether the risks to individuals participating in the clinical trials are minimized and are reasonable in relation to anticipated benefits. The IRB also approves the form and content of the informed consent, which must be signed by each clinical trial patient or his or her legal representative, and must monitor the clinical trial until completed. Clinical trials involving biological product candidates also must be reviewed by an IBC, a local institutional committee that reviews and oversees basic and clinical research conducted at that institution. The IBC assesses the safety of the research and identifies any potential risk to public health or the environment.

Human clinical trials are typically conducted in three sequential phases that may overlap or be combined:

- *Phase 1*. The investigational product candidate is initially introduced into healthy human patients and tested for safety. In the case of some products for severe or life-threatening diseases, especially when the product candidate may be inherently too toxic to be ethically administered to healthy volunteers, the initial human testing is often conducted in patients; gene therapy is usually administered to patients in Phase 1 trials. This is also true in situations where toxicity can only be judged in patients with disease. An evaluation for preliminary evidence of efficacy can be performed at this time.
- *Phase 2*. The investigational product candidate is evaluated in a limited patient population to identify possible adverse effects and safety risks, to evaluate preliminarily the efficacy of the product candidate for specific targeted diseases, and to generate hypotheses for the dosage tolerance, optimal dosage, and dosing schedule.
- *Phase 3*. Clinical trials are undertaken to evaluate further dosage, clinical efficacy, potency, and safety in an expanded patient population at geographically dispersed clinical trial sites. These clinical trials are intended to establish the overall risk/benefit ratio of the product candidate and provide an adequate basis for product labeling.

Post-approval clinical trials, sometimes referred to as Phase 4 clinical trials, may be conducted after initial marketing approval. These clinical trials are used to gain additional experience from the treatment of patients in the intended therapeutic indication, particularly for long-term safety follow-up. The FDA recommends that sponsors observe patients for potential gene therapy-related delayed adverse events with agents such as those we are developing for a period of up to 15 years, including a minimum of five years of annual examinations followed by ten years of annual queries, either in person or by questionnaire, of clinical trial patients.

During all phases of clinical development, regulatory agencies require extensive monitoring and auditing of all clinical activities, clinical data, and clinical trial investigators. Annual progress reports detailing the results of the clinical trials must be submitted to the FDA. Written IND safety reports must be promptly submitted to the FDA and the investigators for serious and unexpected adverse events, any findings from other trials, tests in laboratory animals or *in vitro* testing that suggest a significant risk for human patients, or any clinically important increase in the rate of a serious suspected adverse reaction over that listed in the protocol or investigator brochure. The sponsor must submit an IND safety report within 15 calendar days after the sponsor determines that the information qualifies for expedited reporting. The sponsor also must notify the FDA of any unexpected fatal or life-threatening suspected adverse reaction within seven calendar days after the sponsor's initial receipt of the information. Phase 1, Phase 2, and Phase 3 clinical trials may not be completed successfully within any specified period, if at all. The FDA, the sponsor, or its data safety monitoring board may suspend a clinical trial at any time on various grounds, including a finding that the patients are being exposed to an unacceptable health risk. Similarly, an IRB can suspend or terminate approval of a clinical trial at its institution if the clinical trial is not being conducted in accordance with the IRB's requirements or if the investigational product candidate has been associated with unexpected serious harm to patients.

There are also requirements governing the reporting of ongoing clinical trials and completed clinical trial results to public registries. Sponsors of clinical trials of FDA-regulated products, including biologics, are required to register and disclose certain clinical trial information, which is publicly available at www.clinicaltrials.gov. Information related to the product, patient population, phase of investigation, study sites and investigators, and other aspects of the clinical trial is then made public as part of the registration. Sponsors are also obligated to discuss the results of their clinical trials after completion. Disclosure of the results of these trials can be delayed until the new product or new indication being studied has been approved.

Concurrent with clinical trials, companies usually complete additional animal studies and also develop additional information about the physical characteristics of the components of a combination product as well as finalize processes for manufacturing the components in commercial quantities in accordance with cGMP requirements. To help reduce the risk of the introduction of adventitious agents with use of biological products, the PHS Act emphasizes the importance of manufacturing control for products whose attributes cannot be precisely defined. The manufacturing process must be capable of consistently producing quality batches of the product candidate and, among other things, the sponsor must develop methods for testing the identity, strength, quality, potency and purity of the final product. Additionally, appropriate packaging must be selected and tested and stability studies must be conducted to demonstrate that the components of a combination product candidate do not undergo unacceptable deterioration over their shelf life.

U.S. Review and Approval Processes

After the completion of clinical trials of an investigational biologic product, FDA approval of a BLA must be obtained before commercial marketing of the product. The BLA must include results of product development, laboratory, and animal studies, human trials, information on the manufacture and composition of the product, proposed labeling and other relevant information. In addition, under the Pediatric Research Equity Act, or PREA, a BLA or supplement to a BLA must contain data to assess the safety and effectiveness of the combination product for the claimed indications in all relevant pediatric subpopulations and to support dosing and administration for each pediatric subpopulation for which the product is safe and effective. The FDA may grant deferrals for submission of data or full or partial waivers. Unless otherwise required by regulation, PREA does not apply to any product for an

indication for which orphan Designation has been granted. Currently we have Orphan-Drug Designation for Toca 511 & Toca FC for the treatment of malignant glioma in addition to GBM. The testing and approval processes require substantial time and effort and there can be no assurance that the FDA will accept the BLA for filing and, even if filed, that any approval will be granted on a timely basis, if at all.

Under the Prescription Drug User Fee Act, or PDUFA, as amended, each BLA must be accompanied by a significant user fee. The FDA adjusts the PDUFA user fees on an annual basis. PDUFA also imposes annual program fees on prescription drugs or biologics. Fee waivers or reductions are available in certain circumstances, including a waiver of the application fee for the first application filed by a small business. Additionally, no user fees are assessed on BLAs for products designated as orphan drugs, unless the application also includes a non-orphan indication.

Within 60 days following submission of the application, the FDA reviews a BLA to determine if it is substantially complete before the agency accepts it for filing. The FDA may refuse to file any BLA that it deems incomplete or not properly reviewable at the time of submission and may request additional information. In this event, the BLA must be resubmitted with the additional information. The resubmitted application also is subject to an initial filing review before the FDA accepts it for filing. Once the submission is accepted for filing, the FDA begins an in-depth substantive review of the BLA. The FDA reviews the BLA to determine, among other things, whether the proposed product is safe and potent, or effective, for its intended use, and has an acceptable purity profile, and whether the product is being manufactured in accordance with cGMP to assure and preserve the product's identity, safety, strength, quality, potency and purity. The FDA may refer applications for novel products or products that present difficult questions of safety or efficacy to an advisory committee, typically a panel that includes clinicians and other experts, for review, evaluation and a recommendation as to whether the application should be approved and under what conditions. The FDA is not bound by the recommendations of an advisory committee, but it considers such recommendations carefully when making decisions. During the product approval process, the FDA also will determine whether a REMS is necessary to assure the safe use of the product. If the FDA concludes that a REMS is needed, the sponsor of the BLA must submit a proposed REMS; the FDA will not approve the BLA without a REMS, if required.

Before approving a BLA, the FDA will inspect the facilities at which the product is manufactured. The FDA will not approve the product unless it determines that the manufacturing processes and facilities are in substantial compliance with cGMP requirements and adequate to assure consistent production of the product within required specifications. Additionally, before approving a BLA, the FDA will typically inspect one or more clinical sites, to assure that the clinical trials were conducted in compliance with GCP requirements. To assure cGMP, GLP and GCP compliance, an applicant must incur significant expenditure of time, money, and effort in the areas of training, record keeping, production, and quality control.

Notwithstanding the submission of relevant data and information, the FDA may ultimately decide that the BLA does not satisfy its regulatory criteria for approval and deny approval. Data obtained from clinical trials are not always conclusive and the FDA may interpret data differently from how we interpret the same data. If the agency decides not to approve the BLA in its present form, the FDA will issue a complete response letter that usually describes all of the specific deficiencies in the BLA identified by the FDA. The deficiencies identified may be minor, for example, requiring labeling changes, or major, for example, requiring additional clinical trials. Additionally, the complete response letter may include recommended actions that the applicant might take to place the application in a condition for approval. If a complete response letter is issued, the applicant may either resubmit the BLA, addressing all of the deficiencies identified in the letter, or withdraw the application.

If a product candidate receives regulatory approval, the approval may be significantly limited to specific diseases and dosages or the indications for use may otherwise be limited, which could restrict the commercial value of the product. Further, the FDA may require that certain contraindications, warnings, or precautions be included in the product labeling. The FDA may impose restrictions and conditions on product distribution, prescribing, or dispensing in the form of a REMS, or otherwise limit the scope of any approval. In addition, the FDA may require post marketing clinical trials, sometimes referred to as Phase 4 clinical trials, designed to assess further a biological product's safety and effectiveness, and testing and surveillance programs to monitor the safety of approved products that have been commercialized.

One of the performance goals agreed to by the FDA under the PDUFA is to review 90% of original standard BLAs within 10 months of the 60 day filing date and 90% of original priority BLAs within six months of the 60 day filing date, whereupon a review decision is to be made. The FDA does not always meet its PDUFA goal dates for standard and priority BLAs and its review goals are subject to change from time to time. A major amendment (a significant amount of new information, new analyses, new study or trial report) can extend the review period (PDUFA goal date) by three months. The FDA may either decide to extend the review period or defer the review to a subsequent review cycle.

Orphan-Drug Designation

Under the Orphan-Drug Act, the FDA may grant orphan designation to a drug or biological product intended to treat a rare disease or condition, which is generally a disease or condition that affects fewer than 200,000 individuals in the United States, or more than 200,000 individuals in the United States for which there is no reasonable expectation that the cost of developing and making a drug or biological product available in the United States for this type of disease or condition will be recovered from sales of the product. Orphan product designation must be requested before submitting a BLA. After the FDA grants orphan product designation, the identity of the therapeutic agent and its potential orphan use are disclosed publicly by the FDA. We have been granted Orphan-Drug Designation by the FDA for Toca 511 & Toca FC for the treatment of malignant glioma in addition to GBM, the indication that we are initially pursuing. Orphan product designation does not convey any advantage in or shorten the duration of the regulatory review and approval process. There can be no assurance that we will receive Orphan-Drug Designation for additional indications or for any additional product candidates.

If a product candidate that has orphan designation subsequently receives the first FDA approval for the disease or condition for which it has such designation, the product is entitled to orphan product exclusivity, which means that the FDA may not approve any other applications to market the same drug or biological product for the same indication for seven years, except in limited circumstances, such as a showing of clinical superiority to the product with orphan exclusivity. Competitors, however, may receive approval of different products for the indication for which the orphan product has exclusivity or obtain approval for the same product but for a different indication for which the orphan product has exclusivity. Orphan product exclusivity also could block the approval of one of our products for seven years if a competitor obtains approval of the same biological product as defined by the FDA or if our product candidate is determined to be contained within the competitor's product for the same indication or disease. If a drug or biological product designated as an orphan product receives marketing approval for an indication broader than what is designated, it may not be entitled to orphan product exclusivity. The Committee of Orphan Medicinal Products of the EMA has designated both flucytosine and vocimagene amiretrorepvec as orphan medicinal products indicated for the treatment of glioma. Orphan designation provides for a full waiver of Scientific Advice/Protocol Assistance fees in conjunction with small-medium enterprise designation. Also included is a waiver of the fee for a marketing authorization application, and a 10-year market exclusivity upon approval which protects from market competition for similar medicines with similar indications.

Expedited Development and Review Programs

The FDA has four programs in place intended to facilitate and expedite development and review of new drugs and biologics intended to address unmet medical needs in the treatment of serious or life-threatening conditions: Fast Track Designation, Breakthrough Therapy Designation, accelerated approval, and priority review designation.

The Fast Track program is intended to expedite or facilitate the process for reviewing a new product if it is intended for the treatment of a serious or life-threatening disease or condition, and it demonstrates the potential to address unmet medical needs for such a disease or condition. Fast Track Designation applies to the combination of the product and the specific indication for which it is being studied. The sponsor of a new drug or biologic may request the FDA to designate the drug or biologic as a Fast Track product at any time during the clinical development of the product. Unique to a Fast Track product, the FDA may consider for review sections of the marketing application on a rolling basis before the complete application is submitted, if the sponsor provides a schedule for the submission of the sections of the application, the FDA agrees to accept sections of the application and determines that the schedule is acceptable, and the sponsor pays any required user fees upon submission of the first section of the application. We have received Fast Track Designation of Toca 511 & Toca FC for the treatment of patients with recurrent HGG, to improve their overall survival.

A new product can receive Breakthrough Therapy Designation if it is intended, alone or in combination with one or more other drugs, to treat a serious or life-threatening disease or condition and preliminary clinical evidence indicates that it may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development. A Breakthrough Therapy Designation conveys all of the features of Fast Track Designation in addition to more intensive FDA guidance on an efficient development program, organizational commitment involving senior managers, and eligibility for priority review. Specifically, FDA intends to expedite the development and review of a Breakthrough Therapy by, where appropriate, intensively involving senior managers and experienced review staff in a proactive collaborative, cross-disciplinary review. Where appropriate, FDA also intends to assign a cross-disciplinary project lead for the review team to facilitate an efficient review of the development program. The FDA notes that a compressed drug development program still must generate adequate data to demonstrate that the drug or biologic meets the statutory standard for approval. Omitting components of the development program that are necessary for such a determination can significantly delay, or even preclude, marketing approval.

The FDA has granted Toca 511 & Toca FC Breakthrough Therapy Designation for the treatment of recurrent HGG. Our Breakthrough Therapy Designation application was based on data from three Phase 1 ascending-dose clinical trials involving 127 patients with recurrent brain cancer. The clinical data included results published in Science Translational Medicine, including safety data, patient survival data and data regarding durable, complete or partial tumor shrinkage as determined by independent radiology review. In addition, preclinical information was provided to the FDA supporting a novel immunological mechanism of action involving the depletion of immune-suppressive myeloid cells in the tumor microenvironment.

Breakthrough Therapy Designation indicates that preliminary clinical evidence demonstrates the drug may have substantial improvement on one or more clinically significant endpoints over available therapy. Breakthrough Therapy Designation intensifies FDA involvement to ensure an efficient drug development program and is an organizational commitment from the FDA to involve its senior managers. When Breakthrough Therapy Designation has been granted, the FDA is encouraged to meet regularly with the sponsor and subsequent meetings are considered Type B meetings and are established based on the needs of the program.

The FDA may grant Accelerated Approval to a product candidate for a serious or life-threatening condition upon a determination that the product candidate has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit, or an effect on a clinical endpoint that can be measured earlier than an effect on irreversible morbidity or mortality, that is reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit, taking into account the severity, rarity, or prevalence of the condition and the availability or lack of alternative treatments. Accelerated approval is usually contingent on a sponsor's agreement to conduct adequate and well-controlled additional post-approval trials to verify and describe the product's clinical benefit. In addition, the FDA currently requires as a condition for accelerated approval pre-approval of promotional materials, which could adversely impact the timing of the commercial launch of the product.

The EMA has granted Toca 511 & Toca FC PRIME Designation for the treatment of patients with HGG. To be eligible for PRIME Designation, a medicine must show a potential to benefit patients with unmet medical needs based on early clinical data that indicate the treatment may offer a major therapeutic advantage over existing therapies. Through PRIME, EMA provides enhanced interaction to optimize development plans and enable accelerated assessments of applications for marketing authorization.

Fast Track Designation, Breakthrough Therapy Designation, PRIME Designation and accelerated approval do not change the standards for approval but may expedite the development process.

An application for a product candidate may be eligible to obtain Priority Review Designation if it is intended to treat a serious condition and, if approved, would provide a significant improvement in safety or effectiveness. The FDA will attempt to direct additional resources to the evaluation of an application for a new product designated for priority review in an effort to facilitate the review. Priority Review Designation does not change the standards for approval but may expedite the review process. The PDUFA goal for Priority Review is 6 months from filing (8 months from complete submission), instead of 10 months (12 months from complete submission) for a Standard Review.

Post-Approval Requirements

Maintaining post-approval compliance with applicable federal, state, and local statutes and regulations requires the expenditure of substantial time and financial resources. Rigorous and extensive FDA regulation of combination products continues after approval, particularly with respect to cGMP. We rely, and expect to continue to rely, on third parties for the production and distribution of clinical and commercial quantities of any products that we may commercialize. Manufacturers of our products are required to comply with applicable requirements in the cGMP regulations, including quality control and quality assurance and maintenance of records and documentation. Other post-approval requirements applicable to combination products include reporting of cGMP deviations that may affect the identity, potency, purity and overall safety of a distributed product, record-keeping requirements, reporting of adverse effects, reporting updated safety and efficacy information, and complying with electronic record and signature requirements. After a BLA is approved, the product also may be subject to official lot release. As part of the manufacturing process, the manufacturer is required to perform certain tests on each lot of the product before it is released for distribution. If the product is subject to official release by the FDA, the manufacturer submits samples of each lot of product to the FDA together with a release protocol showing a summary of the history of manufacture of the lot and the results of all of the manufacturer's tests performed on the lot. The FDA also may perform certain confirmatory tests on lots of some products, such as viral vaccines, before releasing the lots for distribution by the manufacturer. In addition, the FDA conducts laboratory research related to the regulatory standards on the safety, purity, potency, and effectiveness of combination products.

We also must comply with the FDA's advertising and promotion requirements, such as those related to direct-to-consumer advertising, the prohibition on promoting products for uses or in patient populations that are not described in the product's approved labeling (known as "off-label use"), industry-sponsored scientific and educational activities, and promotional activities involving the internet. Discovery of previously unknown problems or the failure to comply with the applicable regulatory requirements may result in restrictions on the marketing of a product or withdrawal of the product from the market as well as possible civil or criminal sanctions. Failure to comply with the applicable U.S. requirements at any time during the product development process, approval

process or after approval, may subject an applicant or manufacturer to administrative or judicial civil or criminal sanctions and adverse publicity. FDA sanctions could include refusal to approve pending applications, withdrawal of an approval, clinical hold, warning or untitled letters, product recalls, product seizures, total or partial suspension of production or distribution, injunctions, fines, refusals of government contracts, mandated corrective advertising or communications with doctors, debarment, restitution, disgorgement of profits, or civil or criminal penalties. Any agency or judicial enforcement action could have a material adverse effect on us.

Manufacturers and other entities involved in the manufacture and distribution of approved products are required to register the establishments where the approved products are made with the FDA and certain state agencies, and are subject to periodic unannounced inspections by the FDA and certain state agencies for compliance with cGMPs and other laws. Accordingly, manufacturers must continue to expend time, money, and effort in the area of production and quality control to maintain cGMP compliance. Discovery of problems with a product after approval may result in restrictions on a product, manufacturer, or holder of an approved BLA, including withdrawal of the product from the market. In addition, changes to the manufacturing process or facility generally require prior FDA approval before being implemented. Other types of changes to the approved product, such as adding new indications and additional labeling claims, are also subject to further FDA review and approval.

U.S. Patent Term Restoration

Depending upon the timing, duration, and specifics of the FDA approval of the use of our product candidates, some of our U.S. patents may be eligible for limited patent term extension under the Drug Price Competition and Patent Term Restoration Act of 1984, commonly referred to as the Hatch-Waxman Amendments. The Hatch-Waxman Amendments permit a patent restoration term of up to five years as compensation for patent term lost during product development and the FDA regulatory review process. However, patent term restoration cannot extend the remaining term of a patent beyond a total of 14 years from the product's approval date. The patent term restoration period is generally one-half the time between the effective date of an IND and the submission date of a BLA plus the time between the submission date of a BLA and the approval of that application. Only one patent applicable to an approved biological product is eligible for the extension and the application for the extension must be submitted prior to the expiration of the patent. The U.S. Patent and Trademark Office, in consultation with the FDA, reviews and approves the application for any patent term extension or restoration. In the future, we may intend to apply for restoration of patent term for one of our currently owned or licensed patents to add patent life beyond its current expiration date, depending on the expected length of the clinical trials and other factors involved in the filing of the relevant BLA.

Biosimilars and Exclusivity

The Biologics Price Competition and Innovation Act, or BPCIA, created an abbreviated approval pathway for biological products shown to be highly similar to, or interchangeable with, an FDA-licensed reference biological product.

Biosimilarity, which requires that there be no clinically meaningful differences between the biological product and the reference product in terms of safety, purity, and potency, can be shown through analytical studies, animal studies, and a clinical study or studies. Interchangeability requires that a product is biosimilar to the reference product and the product must demonstrate that it can be expected to produce the same clinical results as the reference product in any given patient and, for products that are administered multiple times to an individual, the biologic and the reference biologic may be alternated or switched after one has been previously administered without increasing safety risks or risks of diminished efficacy relative to exclusive use of the reference biologic.

The BPCIA includes, among other provisions:

- A 12-year exclusivity period from the date of first licensure of the reference product, during which approval of a 351(k) application referencing that product may not be made effective;
- A four-year exclusivity period from the date of first licensure of the reference product, during which a 351(k) application referencing that product may not be submitted; and
- An exclusivity period for certain biological products that have been approved through the 351(k) pathway as interchangeable biosimilars;

The BPCIA also establishes procedures for identifying and resolving patent disputes involving applications submitted under section 351(k) of the PHS Act.

A biological product can also obtain pediatric market exclusivity in the United States. Pediatric exclusivity, if granted, adds six months to existing exclusivity periods and patent terms. This six-month exclusivity, which runs from the end of other exclusivity protection or patent term, may be granted based on the voluntary completion of a pediatric clinical trial in accordance with an FDA-issued "Written Request" for such a clinical trial.

Additional U.S. Regulation

In addition to the foregoing, state and federal laws regarding environmental protection and hazardous substances, including the Occupational Safety and Health Act, the Resource Conservancy and Recovery Act and the Toxic Substances Control Act, may affect our business. These and other laws govern our use, handling and disposal of various biological, chemical, and radioactive substances used in, and wastes generated by, our operations. If our operations result in contamination of the environment or expose individuals to hazardous substances, we could be liable for damages and governmental fines. We believe that we are in material compliance with applicable environmental laws and that continued compliance therewith is unlikely to have a material adverse effect on our business. We cannot predict, however, how changes in these laws may affect our future operations.

Federal and State Fraud and Abuse Laws

In the United States, our current and future operations are potentially subject to regulation by various federal, state and local authorities in addition to the FDA, including but not limited to the Centers for Medicare and Medicaid Services, or CMS, other divisions of the U.S. Department of Health and Human Services, or HHS, for instance, the Office of Inspector General, U.Sl Department of Justice, or DOJ, and individual U.S. Attorney offices within the DOJ, and state and local governments. These federal and state laws, some of which may not be applicable to us or our product candidates unless and until we obtain FDA marketing approval for any of our product candidates, include, among others, the anti-fraud and abuse provisions of the Social Security Act, which our sales, marketing and scientific/educational grant programs must comply with, false claims statutes, transparency laws, the privacy and security provisions of the Health Insurance Portability and Accountability Act, or HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act, or HITECH, laws and regulation regarding providing drug samples, sales and marketing activities and our relationships with customers and payors as follows.

The federal Anti-Kickback Statute prohibits, among other things, individuals and entities from knowingly and willfully offering, paying, soliciting, or receiving any remuneration, directly or indirectly, overtly or covertly, to induce or in return for purchasing, leasing, recommending, ordering, or arranging for the purchase, lease, recommendation or order of any health care item, good, facility or service reimbursable, in whole or in part, under Medicare, Medicaid, or other federally financed healthcare programs. This statute has been interpreted to apply to arrangements between pharmaceutical manufacturers on one hand and prescribers, purchasers, formulary managers and other individuals and entities on the other. Although there are a number of statutory exemptions and regulatory safe harbors protecting certain common activities from prosecution, the exceptions and safe harbors are drawn narrowly and require strict compliance in order to offer protection. Practices that involve remuneration that may be alleged to be intended to induce prescribing, purchases, or recommendations may be subject to scrutiny if they do not qualify for an exception or safe harbor. Additionally, the intent standard under the federal Anti-Kickback Statute was amended by the Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act of 2010, or collectively, the Affordable Care Act, to a stricter standard such that a person or entity does not need to have actual knowledge of the statute or specific intent to violate it in order to have committed a violation. Further, the Affordable Care Act codified case law that a claim including items or services resulting from a violation of the federal Anti-Kickback Statute constitutes a false or fraudulent claim for purposes of the federal civil False Claims Act.

HIPAA created additional federal criminal statutes that prohibit, among other actions, knowingly and willfully executing, or attempting to execute, a scheme to defraud or to obtain, by means of false or fraudulent pretenses, representations or promises, any money or property owned by, or under the control or custody of, any healthcare benefit program, including private third-party payers, willfully obstructing a criminal investigation of a healthcare offense, and knowingly and willfully falsifying, concealing or covering up by trick, scheme or device, a material fact or making any materially false, fictitious or fraudulent statement in connection with the delivery of or payment for healthcare benefits, items or services. Similar to the federal Anti-Kickback Statute, a person or entity does not need to have actual knowledge of the statute or specific intent to violate it in order to have committed a violation.

Federal false claims and civil monetary penalties laws, including the federal civil False Claims Act, prohibit, among other things, any person or entity from knowingly presenting, or causing to be presented, a false, fictitious or fraudulent claim for payment to, or approval by, the federal government, or knowingly making, using, or causing to be made or used, a false statement to get a false claim paid. Several pharmaceutical and other health care companies have been prosecuted under these laws for allegedly providing free product to customers with the expectation that the customers would bill federal programs for the product. Other companies have been prosecuted for causing false claims to be submitted because of the company's marketing of the product for unapproved or off-label, and thus non-reimbursable, uses.

The majority of states also have statutes or regulations similar to the federal Anti-Kickback Statute and false claims laws, which apply to items and services, reimbursed under Medicaid and other state programs, or, in several states, apply regardless of the payor.

We may also be subject to data privacy and security regulations by both the federal government and the states in which we conduct our business. HIPAA, as amended by HITECH, and their respective implementing regulations, including the final Omnibus Rule published on January 25, 2013, imposes requirements on certain types of entities, known as covered entities, including certain healthcare providers, health plans, and healthcare clearinghouses, such as mandatory contractual terms, relating to the privacy, security, and transmission of individually identifiable health information. Among other things, HITECH makes HIPAA's security standards and certain privacy standards directly applicable to business associates, which are independent contractors or agents of covered entities that create, receive, maintain or transmit protected health information in connection with providing a service for or on behalf of a covered entity. HITECH also created four new tiers of civil monetary penalties, amended HIPAA to make civil and criminal penalties directly applicable to business associates, and gave state attorneys general new authority to file civil actions for damages or injunctions in federal courts to enforce the federal HIPAA laws and seek attorneys' fees and costs associated with pursuing federal civil actions. In addition, many state laws govern the privacy and security of health information in specified circumstances, many of which differ from each other and from HIPAA in significant ways and may not have the same requirements, thus complicating compliance efforts.

Additionally, the federal Physician Payments Sunshine Act under the Affordable Care Act, and its implementing regulations, require that certain manufacturers of drugs, devices, biological and medical supplies for which payment is available under Medicare, Medicaid or the Children's Health Insurance Program, with certain exceptions, annually report to CMS information related to certain payments or other transfers of value made or distributed to physicians (defined to include doctors, dentists, optometrists, podiatrists and chiropractors) and teaching hospitals, or to entities or individuals at the request of, or designated on behalf of, the physicians and teaching hospitals and to report annually certain ownership and investment interests held by physicians and their immediate family members.

Further, some state, local and foreign laws require pharmaceutical companies to comply with the pharmaceutical industry's voluntary compliance guidelines and the relevant compliance guidance promulgated by the federal government; restrict payments that may be made to healthcare providers and other potential referral sources, and/or require drug manufacturers to report information related to payments and transfers of value made to physicians and other health care providers or entities, or marketing expenditures; require the licensure of sales representatives; require drug manufacturers to report information related to drug pricing; data privacy and security laws and regulations in foreign jurisdictions that may be more stringent than those in the United States (such as the European Union, which adopted the General Data Protection Regulation, which became effective in May 2018); and laws governing the privacy and security of health information in certain circumstances, many of which differ from each other in significant ways and may not have the same effect, thus complicating compliance efforts.

Because of the breadth of these laws and the narrowness of the exceptions and safe harbors, it is possible that some of our business activities could be subject to challenge under one or more of such laws. Such a challenge could have a material adverse effect on our business, financial condition, and results of operations. If our operations are found to be in violation of any of these or any other health regulatory laws that may apply to us, we may be subject to, without limitation, significant sanctions, including the imposition of significant civil, criminal and administrative penalties, damages, monetary fines, disgorgement, individual imprisonment, possible exclusion from participation in Medicare, Medicaid and other federal healthcare programs, contractual damages, reputational harm, diminished profits and future earnings, additional integrity oversight and reporting obligations and curtailment or restructuring of our operations, any of which could adversely affect our ability to operate our business and our results of operations.

In addition, as part of the sales and marketing process, pharmaceutical companies frequently provide samples of approved products to physicians. This practice is regulated by the FDA and other governmental authorities, including, in particular, requirements concerning record keeping and control procedures. Any failure to comply with the regulations may result in significant criminal and civil penalties as well as damage to our credibility in the marketplace.

Coverage and Reimbursement

In many of the markets where we may do business in the future, the prices of pharmaceutical products are subject to direct price controls (by law) and to reimbursement programs with varying price control mechanisms. In the United States, significant uncertainty exists as to the coverage and reimbursement status of any product candidates for which we obtain product approval. A number of gene therapy products have recently been approved by the FDA. Although CMS subsequently approved its first method of coverage and reimbursement for one such product, the methodology has been subject to challenge by members of Congress. Often private payors follow the coverage and reimbursement decisions of the Medicare program, and it is difficult to predict how CMS may decide to cover and reimburse our product candidates, once approved, and those determinations are subject to change.

Moreover, the process for determining whether a third-party payor will provide coverage for a drug product may be separate from the process for setting the price of a drug product or for establishing the reimbursement rate that such a payor will pay for the drug product. Third-party payors may limit coverage to specific products on an approved list, also known as a formulary, which might not include all of the FDA-approved drugs for a particular indication. A decision by a third-party payor not to cover our product candidates could reduce physician utilization of our products once approved. A payor's decision to provide coverage for a drug product does not imply that an adequate reimbursement rate will be approved. Further, one payor's determination to provide coverage for a drug product does not assure that other payors will also provide coverage for the drug product. Coverage and reimbursement for new products can differ significantly from payor to payor. As a result, the coverage determination process will require us to provide scientific and clinical support for the use of our products to each payor separately and will be a time-consuming process. Additionally, third-party reimbursement may not be available or may not be adequate to enable us to maintain price levels sufficient to realize an appropriate return on our investment in product development.

We intend to seek approval to market our product candidates in both the United States and in selected foreign jurisdictions. If we obtain approval in one or more foreign jurisdictions for our product candidates, we will be subject to rules and regulations in those jurisdictions. In some foreign countries, particularly those in the European Union, the pricing of biologics is subject to governmental control and other market regulations which could put pressure on the pricing and usage of our product candidates. In these countries, pricing negotiations with governmental authorities can take considerable time after obtaining marketing approval of a product candidate.

The marketability of any product candidates for which we or our collaborators receive regulatory approval for commercial sale may suffer if the government and third-party payors fail to provide adequate coverage and reimbursement. In addition, an emphasis on cost containment measures in the United States has increased and we expect will continue to increase the pressure on pharmaceutical pricing. Third-party payors are increasingly challenging the prices charged for medical products and services, examining the medical necessity and reviewing the cost-effectiveness of drugs, medical devices and medical services, in addition to questioning safety and efficacy. If these third-party payors do not consider our products to be cost-effective compared to other available therapies, they may not cover our products after FDA approval or, if they do, the level of payment may not be sufficient to allow us to sell our products at a profit. Coverage policies and third-party reimbursement rates may change at any time. Even if favorable coverage and reimbursement status is attained for one or more products for which we or our collaborators receive regulatory approval, less favorable coverage policies and reimbursement rates may be implemented in the future.

Healthcare Reform

In March 2010, President Obama enacted the Affordable Care Act, which has the potential to substantially change healthcare financing and delivery by both governmental and private insurers, and significantly impact the pharmaceutical and biotechnology industry. The Affordable Care Act will impact existing government healthcare programs and may result in the development of new programs.

Among the Affordable Care Act's provisions of importance to the pharmaceutical and biotechnology industries, in addition to those otherwise described above, are the following:

- an annual, nondeductible fee on any entity that manufactures or imports certain specified branded prescription drugs and biologic agents apportioned among these entities according to their market share in some government healthcare programs;
- an increase in the statutory minimum rebates a manufacturer must pay under the Medicaid Drug Rebate Program, to 23.1% and 13% of the average manufacturer price for most branded and generic drugs, respectively and capped the total rebate amount for innovator drugs at 100% of the Average Manufacturer Price, or AMP;
- a new methodology by which rebates owed by manufacturers under the Medicaid Drug Rebate Program are calculated for certain drugs and biologics, including our product candidates, that are inhaled, infused, instilled, implanted or injected;
- extension of manufacturers' Medicaid rebate liability to covered drugs dispensed to individuals who are enrolled in Medicaid managed care organizations;
- expansion of eligibility criteria for Medicaid programs by, among other things, allowing states to offer Medicaid coverage to additional individuals and by adding new mandatory eligibility categories for individuals with income at or below 133% of the federal poverty level, thereby potentially increasing manufacturers' Medicaid rebate liability;
- a new Medicare Part D coverage gap discount program, in which manufacturers must now agree to offer 70% point-of-sale discounts off negotiated prices of applicable brand drugs to eligible beneficiaries during their coverage gap period, as a condition for the manufacturer's outpatient drugs to be covered under Medicare Part D;
- expansion of the entities eligible for discounts under the Public Health Service pharmaceutical pricing program;

- a new Patient-Centered Outcomes Research Institute to oversee, identify priorities in, and conduct comparative clinical effectiveness research, along with funding for such research;
- establishment of a Center for Medicare and Medicaid Innovation at CMS to test innovative payment and service delivery models to lower Medicare and Medicaid spending, potentially including prescription drug spending that began on January 1, 2011; and
- a licensure framework for follow on biologic products.

Since its enactment, there have been judicial and Congressional challenges to certain aspects of the Affordable Care Act, as well as recent efforts by the Trump administration to repeal or replace certain aspects of the Affordable Care Act. Since January 2017, President Trump has signed two Executive Orders and other directives designed to delay the implementation of certain provisions of the Affordable Care Act or otherwise circumvent some of the requirements for health insurance mandated by the Affordable Care Act. Concurrently, Congress has considered legislation that would repeal or repeal and replace all or part of the Affordable Care Act. While Congress has not passed comprehensive repeal legislation, two bills affecting the implementation of certain taxes under the Affordable Care Act have been signed into law. Legislation enacted in 2017, informally the Tax Cuts and Jobs Act, or Tax Act, included a provision repealing, effective January 1, 2019, the tax-based shared responsibility payment imposed by the Affordable Care Act on certain individuals who fail to maintain qualifying health coverage for all or part of a year that is commonly referred to as the "individual mandate". On January 22, 2018, President Trump signed a continuing resolution on appropriations for fiscal year 2018 that delayed the implementation of certain Affordable Care Act-mandated fees, including the so-called "Cadillac" tax on certain high cost employer-sponsored insurance plans, the annual fee imposed on certain health insurance providers based on market share, and the medical device excise tax on non-exempt medical devices. The Bipartisan Budget Act of 2018, or the BBA, among other things, amended the Affordable Care Act, effective January 1, 2019, to close the coverage gap in most Medicare Part D drug plans, commonly referred to as the "donut hole". In July 2018, CMS published a final rule permitting further collections and payments to and from certain Affordable Care Act qualified health plans and health insurance issuers under the Affordable Care Act risk adjustment program in response to the outcome of federal district court litigation regarding the method CMS uses to determine this risk adjustment. On December 14, 2018, a Texas U.S. District Court Judge ruled that the Affordable Care Act is unconstitutional in its entirety because the "individual mandate" was repealed by Congress as part of the Tax Act. While the Texas U.S. District Court Judge, as well as the Trump administration and CMS, have stated that the ruling will have no immediate effect pending appeal of the decision, it is unclear how this decision, subsequent appeals, and other efforts to repeal and replace the Affordable Care Act will impact the Affordable Care Act.

Other legislative changes have been proposed and adopted in the United States since the Affordable Care Act was enacted. For example, in August 2011, the Budget Control Act of 2011, among other things, created measures for spending reductions by Congress. A Joint Select Committee on Deficit Reduction, tasked with recommending a targeted deficit reduction of at least $1.2 trillion for the fiscal year 2012 through 2021, was unable to reach required goals, thereby triggering the legislation's automatic reduction to several government programs. This includes aggregate reductions of Medicare payments to providers of up to 2% per fiscal year, which went into effect in April 2013 and, due to subsequent legislation, including the BBA, will remain in effect through 2027 unless additional Congressional action is taken. Further, in January 2013, President Obama signed into law the American Taxpayer Relief Act of 2012, which, among other things, further reduced Medicare payments to several providers, including hospitals, imaging centers and cancer treatment centers, and increased the statute of limitations period for the government to recover overpayments to providers from three to five years.

In addition, there has been heightened governmental scrutiny in the United States of pharmaceutical pricing practices in light of the rising cost of prescription drugs and biologics. Such scrutiny has resulted in several recent Congressional inquiries and proposed and enacted federal and state legislation designed to, among other things, bring more transparency to product pricing, review the relationship between pricing and manufacturer patient programs, and reform government program reimbursement methodologies for products. At the federal level, the Trump administration's budget proposal for fiscal year 2019 contains further product price control measures that could be enacted during the 2019 budget process or in other future legislation, including, for example, measures to permit Medicare Part D plans to negotiate the price of certain products under Medicare Part B, to allow some states to negotiate product prices under Medicaid, and to eliminate cost sharing for generic products for low-income patients. Additionally, the Trump administration released a "Blueprint" to lower drug prices and reduce out of pocket costs of drugs that contains additional proposals to increase manufacturer competition, increase the negotiating power of certain federal healthcare programs, incentivize manufacturers to lower the list price of their products and reduce the out of pocket costs of drug products paid by consumers. HHS has already started the process of soliciting feedback on some of these measures and, at the same, is immediately implementing others under its existing authority. For example, in September 2018, CMS announced that it will allow Medicare Advantage Plans the option to use step therapy for Part B drugs beginning January 1, 2019, and in October 2018, CMS proposed a new rule that would require direct-to-consumer television advertisements of prescription drugs and biological products, for which payment is available through or under Medicare or Medicaid, to include in the advertisement the Wholesale Acquisition Cost, or list price, of that drug or biological product. On January 31, 2019, the HHS Office of Inspector General proposed modifications to federal Anti-Kickback Statute safe harbors which, among other things, may affect rebates paid by manufacturers to Medicare Part D plans, the purpose of which is to further reduce the cost of drug products to consumers. While a number of these and other proposed measures will require authorization

through additional legislation to become effective, Congress and the Trump administration have each indicated that it will continue to seek new legislative and/or administrative measures to control drug costs. At the state level, legislatures are increasingly passing legislation and implementing regulations designed to control pharmaceutical and biological product pricing, including price or patient reimbursement constraints, discounts, restrictions on certain product access and marketing cost disclosure and transparency measures, and, in some cases, designed to encourage importation from other countries and bulk purchasing.

We anticipate that the Affordable Care Act and other legislative reforms will result in additional downward pressure on the price that we receive for any approved product, if covered, and could seriously harm our business. Any reduction in reimbursement from Medicare and other government programs may result in a similar reduction in payments from private payors. The implementation of cost containment measures or other healthcare reforms may prevent us from being able to generate revenue, attain profitability, or commercialize our products. In addition, it is possible that there will be further legislation or regulation that could harm our business, financial condition, and results of operations.

Environmental Regulation

In addition to the foregoing, state and federal laws regarding environmental protection and hazardous substances, including the Occupational Safety and Health Act, the Resource Conservancy and Recovery Act and the Toxic Substances Control Act, may affect our business. These and other laws govern our use, handling and disposal of various biological, chemical, and radioactive substances used in, and wastes generated by, our operations. If our operations result in contamination of the environment or expose individuals to hazardous substances, we could be liable for damages and governmental fines. We believe that we are in material compliance with applicable environmental laws and that continued compliance therewith is unlikely to have a material adverse effect on our business. We cannot predict, however, how changes in these laws may affect our future operations.

U.S. Foreign Corrupt Practices Act

The U.S. Foreign Corrupt Practices Act, to which we are subject, prohibits corporations and individuals from engaging in certain activities to obtain or retain business or to influence a person working in an official capacity. It is illegal to pay, offer to pay or authorize the payment of anything of value to any foreign government official, government staff member, political party, or political candidate in an attempt to obtain or retain business or to influence otherwise a person working in an official capacity.

Government Regulation Outside of the United States

In addition to regulations in the United States, we will be subject to a variety of regulations in other jurisdictions governing, among other things, clinical trials and any commercial sales and distribution of our products. Because biologically sourced raw materials are subject to unique contamination risks, their use may be subjected to different types of restrictions in different countries.

Whether or not we obtain FDA approval for a product, we must obtain the required approvals from regulatory authorities in foreign countries prior to the commencement of clinical trials or marketing of the product in those countries. Certain countries outside of the United States have a similar process that requires the submission of a clinical trial application equivalent to an IND prior to the commencement of human clinical trials. In the European Union, for example, a clinical trial authorization, or CTA, must be submitted to each country's national health authority and an independent ethics committee, much like the FDA and the IRB, respectively. Once the CTA is approved in accordance with a country's requirements, clinical trials may start.

The requirements and process governing the conduct of clinical trials, product licensing, pricing, and reimbursement vary from country to country. In all cases, the clinical trials are to be conducted in accordance with GCP, applicable regulatory requirements, and the ethical principles that have their origin in the Declaration of Helsinki.

If we fail to comply with applicable foreign regulatory requirements, we may be subject to, among other things, fines, suspension, or withdrawal of regulatory approvals, product recalls, seizure of products, operating restrictions and criminal prosecution in those countries.

Employees

As of December 31, 2018, we had 79 full-time employees. Of these full-time employees, 63 employees are engaged in research and development activities and 16 employees are engaged in finance and general management activities including accounting, contracts, human resources, information technology, investor relations, marketing and business development.

Corporate Information

We were incorporated in Delaware in August 2007. Our principal executive offices are located at 4242 Campus Point Court, Suite 500, San Diego, California 92121. Our telephone number is (858) 412-8400. Our website address is www.tocagen.com.

This Annual Report on Form 10-K, our Quarterly Reports on Form 10-Q, Current Reports on Form 8-K, and any amendments to those reports filed or furnished pursuant to Sections 13(a) and 15(d) of the Securities Exchange Act of 1934, as amended, or the Exchange Act, are available (free of charge) on our website as soon as reasonably practicable after we electronically file such material with, or furnish it to, the Securities and Exchange Commission, or SEC.

Information contained on, or that can be accessed through, our website or social medial sites does not constitute part of this Annual Report on Form 10-K or any other report or document we file with the SEC, and any references to our website and social media sites are intended to be inactive textual references only.

Tocagen, the Tocagen logo and other trademarks or service marks of Tocagen are the property of Tocagen. Other service marks, trademarks, and tradenames referred to in this Annual Report on Form 10-K are the property of their respective owners. Except as set forth above and solely for convenience, the trademarks and tradenames in this Annual Report on Form 10-K are referred to without the ® and ™ symbols, but such references should not be construed as any indicator that their respective owners will not assert, to the fullest extent under applicable law, their rights thereto.

We are an "emerging growth company" as defined in the JOBS Act. We will remain an emerging growth company until the earliest of (i) the last day of our first fiscal year in which we have total annual gross revenues of $1 billion or more, (ii) the date on which we are deemed to be a "large accelerated filer" under the rules of the SEC with at least $700 million of outstanding equity securities held by non-affiliates, (iii) the date on which we issued more than $1 billion in non-convertible debt during the previous three years, or (iv) December 31, 2022. References herein to "emerging growth company" are intended to have the meaning associated with it in the JOBS Act.

Item 1A. Risk Factors

You should carefully consider the following risk factors, as well as the other information in this report, before deciding whether to purchase, hold or sell shares of our common stock. The occurrence of any of the following risks could harm our business, financial condition, results of operations and/or growth prospects or cause our actual results to differ materially from those contained in forward-looking statements we have made in this report and those we may make from time to time. You should consider all of the factors described in this section as well as those discussed in "Management's Discussion and Analysis of Financial Condition and Results of Operations" and our financial statements and the related notes when evaluating our business. If any of the following risks actually occurs, our business, financial condition, results of operations and future growth prospects would likely be materially and adversely affected. In these circumstances, the market price of our common stock would likely decline and you may lose all or part of your investments. Additional risks and uncertainties not presently known to us or that we currently deem immaterial also may impair our business operations.

Risks related to our business and industry

We have incurred significant losses since our inception and anticipate that we will continue to incur significant losses for the foreseeable future.

We are a clinical-stage company with a limited operating history. We are not profitable and have incurred net losses in each year since our inception in 2007, including net losses of $49.0 million, $38.9 million and $33.5 million for the years ended December 31, 2018, 2017 and 2016, respectively. As of December 31, 2018 we had an accumulated deficit of $215.9 million.

We have devoted most of our financial resources to research and development, including our clinical, preclinical and platform development activities. To date, we have financed our operations primarily through the private placement of our convertible preferred stock, our public offerings of our common stock, term loans, the issuance of convertible promissory notes and upfront and milestone payments under our license and collaboration agreements. We expect to continue to incur significant expenses and increasing operating losses for the foreseeable future. The amount of our future net losses will depend, in part, on the rate of our future expenditures and our ability to generate revenue. We have not completed late-stage clinical trials for any product candidate and it will be several years, if ever, before we have a product candidate ready for regulatory approval and commercialization. Even if we or our strategic partners succeed in obtaining regulatory approval and commercializing one or more of our product candidates, we will continue to incur substantial research and development and other expenditures to develop and market additional product candidates. We may encounter unforeseen expenses, difficulties, complications, delays and other unknown factors that may adversely affect our business. The size of our future net losses will depend, in part, on the rate of future growth of our expenses and our ability to generate revenue. Our prior losses and expected future losses have had and will continue to have an adverse effect on our stockholders' equity and working capital.

We will require substantial additional financing to achieve our goals, which may not be available on acceptable terms, or at all. Failure to obtain this necessary capital when needed may force us to delay, limit or terminate our product development efforts or other operations.

We are currently advancing our lead product candidate, Toca 511 & Toca FC, through clinical development and other product candidates through preclinical development. Developing gene therapy products is expensive, and we expect our research and development expenses to continue to increase in connection with our ongoing activities, particularly as we continue to advance our product candidates in clinical trials.

As of December 31, 2018, our cash, cash equivalents and marketable securities were $96.1 million. We expect that our existing cash, cash equivalents and marketable securities as of December 31, 2018 will be sufficient to fund our current operations through at least the next 12 months. However, our operating plan may change as a result of many factors currently unknown to us, and we may need to seek additional funds sooner than planned, through equity and/or debt financings. In November 2018, we entered into an Equity Distribution Agreement with Citigroup Global Markets Inc., or Citigroup, pursuant to which we may sell and issue shares of our common stock having an aggregate offering price of up to $30.0 million from time to time through Citigroup, as our sales agent, or the ATM facility. Other than our ATM facility, we do not have any committed external source of funds. We may also consider new collaborations or selectively partner our technology or programs. In any event, we will require additional capital to obtain regulatory approval for, and to commercialize, our product candidates. Raising funds in the current economic environment may present additional challenges. Even if we believe we have sufficient funds for our current or future operating plans, we may seek additional capital if market conditions are favorable or if we have specific strategic considerations.

Any additional fundraising efforts may divert our management from their day-to-day activities, which may adversely affect our ability to develop and commercialize our product candidates. In addition, we cannot guarantee that future financing will be available in sufficient amounts or on terms acceptable to us, if at all. Subject to limited exceptions, our amended and restated loan and security agreement, or Loan Agreement, also prohibits us from incurring indebtedness without the prior written consent of the lenders. Moreover, the terms of any financing may adversely affect the holdings or the rights of our stockholders and the issuance of additional securities, whether equity or debt, by us, or the possibility of such issuance, may cause the market price of our shares to decline. The sale of additional equity or convertible securities would dilute all of our stockholders. The incurrence of indebtedness would result in increased fixed payment obligations and we may be required to agree to certain restrictive covenants, such as limitations on our ability to incur additional debt, limitations on our ability to acquire, sell or license intellectual property rights and other operating restrictions that could adversely impact our ability to conduct our business. We could also be required to seek funds through arrangements with collaborative partners or otherwise at an earlier stage than otherwise would be desirable and we may be required to relinquish rights to some of our technologies or product candidates or otherwise agree to terms unfavorable to us, any of which may have a material adverse effect on our business, operating results and prospects.

If we are unable to obtain funding on a timely basis, we may be required to significantly curtail, delay or discontinue one or more of our research or development programs or the commercialization of any product candidates or be unable to expand our operations or otherwise capitalize on our business opportunities, as desired, which could materially affect our business, financial condition and results of operations.

Immunotherapy, gene therapy and biopharmaceutical product development is a highly speculative undertaking and involves a substantial degree of uncertainty. We have never generated any revenue from product sales and may never be profitable.

Since our inception in August 2007, we have devoted most of our efforts to developing our gene therapy platform and our lead product candidate, Toca 511 & Toca FC. We are still developing our product candidates, and we have not completed development of any products. Our ability to generate revenue and achieve profitability depends in large part on our ability, alone or with partners, to successfully complete the development of, obtain the necessary regulatory approvals for, and commercialize product candidates. We do not anticipate generating revenues from sales of products for the foreseeable future. Our ability to generate future revenues from product sales depends heavily on our success in:

- completing clinical trials through all phases of clinical development of our current and future product candidates;
- seeking and obtaining marketing approvals for product candidates that successfully complete clinical trials;
- launching and commercializing product candidates for which we obtain marketing approval with a partner or, if launched independently, successfully establishing a sales force, marketing and distribution infrastructure;
- identifying and developing new product candidates;
- progressing our preclinical programs into human clinical trials;
- establishing and maintaining supply and manufacturing relationships with third parties;

- maintaining, protecting, expanding and enforcing our intellectual property; and
- attracting, hiring and retaining qualified personnel.

Because of the numerous risks and uncertainties associated with gene therapy product development, we are unable to predict the timing or amount of increased expenses or when we will be able to achieve or maintain profitability, if ever. In addition, our expenses could increase beyond expectations if we are required by the U.S. Food and Drug Administration, or FDA, or foreign regulatory agencies, to perform studies and clinical trials in addition to those that we currently anticipate or if there are any delays in the development of any of our product candidates. If one or more of the product candidates that we develop is approved for commercial sale, we anticipate incurring significant costs associated with commercializing such product candidates. Even if we are able to generate revenues from the sale of any approved products, we may not become profitable and may need to obtain additional funding to continue operations, which may not be available to us on favorable terms, if at all. Even if we do achieve profitability, we may not be able to sustain or increase profitability on a quarterly or annual basis. Our failure to become and remain profitable would depress the value of our company and could impair our ability to raise capital, expand our business, maintain our research and development efforts, diversify our product offerings or even continue our operations. A decline in the value of our company could also cause stockholders to lose all or part of their investment.

Our gene therapy product candidates are based on novel technology, which makes it difficult to predict the time and cost of product candidate development.

We have concentrated our product research and development efforts on our gene therapy platform, and our future success depends on the successful development of this therapeutic approach. There can be no assurance that any development problems we experience in the future related to our gene therapy platform will not cause significant delays or unanticipated costs, or that such development problems can be solved. We may also experience delays in developing a sustainable, reproducible and scalable manufacturing process or transferring that process to commercial partners, or developing or validating product release assays in a timely manner, which may prevent us from completing our clinical trials or commercializing our products on a timely or profitable basis, if at all.

In addition, the clinical trial requirements of the FDA, the European Medicines Agency, or EMA, and other regulatory agencies and the criteria these regulators use to determine the safety and efficacy of a product candidate vary substantially according to the type, complexity, novelty and intended use and market of the potential products. The regulatory approval process for novel product candidates such as ours can be more expensive and take longer than for other, better known or extensively studied pharmaceutical or other product candidates. The limited precedent for gene therapy approvals makes it difficult to determine how long it will take or how much it will cost to obtain regulatory approvals for our product candidates in the United States, Europe or other territories.

Regulatory requirements governing gene therapy products have changed frequently and may continue to change in the future. For example, in January 2017, the FDA Oncology Center of Excellence, or the Center of Excellence, was created to leverage the combined skills of regulatory scientists and reviewers with expertise in drugs, biologics, and devices (including diagnostics). While the Center of Excellence is designed to help expedite the development of oncology and malignant hematology-related medical products and support an integrated approach in the clinical evaluation of drugs, biologics and devices for the treatment of cancer, the new Center of Excellence may initially create confusion within the FDA and especially in the Center of Biologics and Research that is the primary review division for our initial product candidate. Gene therapy clinical trials conducted at institutions that receive funding for recombinant DNA research from the U.S. National Institutes of Health, or the NIH, are also subject to review by the institution's institutional biosafety committees, or IBC, in addition to the institution's institutional review board, or IRB, to assess the safety of the study before a clinical trial can begin. We have received from time to time questions from the FDA regarding investigational new drug application, or IND, submissions and clinical protocols for Toca 511 & Toca FC. We believe that we have adequately addressed these questions, some of which have caused, in the past, some delays in our clinical trials. Although the FDA decides whether individual gene therapy protocols may proceed, the IRB and IBC review process can impede the initiation of a clinical trial, even if the FDA has reviewed the study and approved its initiation. Conversely, the FDA can put an IND on a partial or complete clinical hold even if the IRB and IBC have provided a favorable review. Our trials have, in the past, been put on hold for reasons including suspected serious adverse events, which resulted in delays of our trials. In addition, adverse developments in clinical trials of gene therapy products conducted by others may cause the FDA or other regulatory bodies to change the requirements for performing studies or for obtaining approval of any of our product candidates.

These regulatory review committees and advisory groups, and the new guidelines they promulgate, may lengthen the regulatory review process, require us to perform additional studies, increase our development costs, lead to changes in regulatory positions and interpretations, delay or prevent approval and commercialization of our product candidates or lead to significant post-approval limitations or restrictions. As we advance our product candidates, we will be required to consult with these regulatory and advisory groups and comply with applicable guidelines. Delay or failure to obtain, or unexpected costs in obtaining, the regulatory approval necessary to bring a potential product to market could decrease our ability to generate sufficient revenue to maintain our business.

We expect to continue to rely on third parties to distribute, manufacture and perform release testing for our vectors, product candidates and other key materials and if such third parties do not carry out their contractual duties or meet expected deadlines, we may not be able to obtain regulatory approvals for our product candidates.

We intend to continue to rely on third-party contract manufacturing organizations, or CMOs, to produce our vectors, product candidates and other key materials and on third-party contract testing organizations, or CTOs, for the establishment and performance of validated product release assays, but we have not entered into commercial supply agreements with any such CMOs or CTOs. Additionally, any CMO may not have experience or availability to produce adequate product candidates at commercial levels and may not achieve the necessary regulatory approvals or produce our vectors and products at the quality, quantities, locations and timing needed to support commercialization. We may change our manufacturing process from the current defined media process to a different defined media process, or from its current equipment to different equipment, or our cell line or vector and there can be no guarantee that the regulatory authorities will approve this new process in a timely manner, or ever. Also, as a consequence of the manufacturing change, there may be a requirement to do more preclinical safety or efficacy studies, develop new manufacturing and release assays and/or repeat all or part of the ascending dose safety study in animals or humans. Regulatory requirements ultimately imposed could adversely affect our ability to test, manufacture or market products.

We have not yet secured manufacturing capabilities for commercial quantities of our viral vector but we intend to rely on third-party manufacturers for commercialization. We may be unable to negotiate binding agreements with our manufacturers to support our commercialization activities at commercially reasonable terms.

No manufacturer we know of currently has the direct experience or the demonstrated ability to produce our vectors and product candidates at reasonable commercial levels or under full commercial requirements. We have developed in-house, a more scalable manufacturing process for Toca 511, which we have transferred to one or more CMOs. We may run into technical or scientific issues related to manufacturing or development that we may be unable to resolve in a timely manner or with available funds. Further, we have not completed the characterization and validation activities necessary for commercial and regulatory approvals. If our manufacturing and testing partners do not satisfy such regulatory requirements, our commercialization efforts may be harmed.

Similarly, we currently have limited manufacturers of the active pharmaceutical ingredient for Toca FC and final drug product. We also rely on outside contractors to perform validated release testing for Toca FC. Currently we have not fully validated production of the drug product, Toca FC.

Even if we have developed manufacturing processes for Toca 511 & Toca FC and successfully implement them at third-party manufacturers, if such third-party manufacturers are unable to produce viral vectors and our product candidates in the necessary quantities, or in compliance with current good manufacturing practices, or cGMP, or in compliance with pertinent regulatory requirements, and within our planned time frame and cost parameters, the development and sales of our products, if approved, may be materially harmed. The facilities used by our contract manufacturers to manufacture our product candidates must be approved by the FDA pursuant to inspections that will be conducted after we submit our BLA to the FDA. We do not directly control the manufacturing process of, and are completely dependent on, our contract manufacturing partners for compliance with cGMPs for the manufacture of our product candidates. If our contract manufacturers cannot successfully manufacture material that conforms to our specifications and the strict regulatory requirements of the FDA or others, they will not be able to secure and/or maintain regulatory approval for their manufacturing facilities. In addition, we have no control over the ability of our contract manufacturers to maintain adequate quality control, quality assurance and qualified personnel. If the FDA or a comparable foreign regulatory authority does not approve these facilities for the manufacture of our product candidates or if it withdraws any such approval in the future, we may need to find alternative manufacturing facilities, which would significantly impact our ability to develop, obtain regulatory approval for or market our product candidates, if approved. In addition, any failure to achieve and maintain compliance with these laws, regulations and standards could subject us to the risk that we may have to suspend the manufacturing of our product candidates or that obtained approvals could be revoked, which would adversely affect our business and reputation.

In addition, any significant disruption in our supplier relationships could harm our business. We source key materials, devices and equipment from third parties, either directly through agreements with suppliers or indirectly through our manufacturers who have agreements with suppliers. There are a small number of suppliers for certain key materials, equipment, software and components that are used to manufacture our product candidates. Such suppliers may not sell these key materials to our manufacturers at the times or quantities we need them or on commercially reasonable terms. We may not have any control over the process, quality or timing of the acquisition of these key materials by our manufacturers.

We also expect to rely on other third parties to store and distribute our vectors and products for our clinical trials. Any performance failure on the part of our distributors could delay clinical development or marketing approval of our product candidates or commercialization of our products, if approved, producing additional losses and depriving us of potential product revenue.

Failure to successfully develop and obtain approval of our lead product candidate, Toca 511 & Toca FC, or our other future product candidates could adversely affect our future success.

Our business and future success is substantially dependent on our ability to obtain regulatory approval of and then successfully commercialize our lead product candidate, Toca 511 & Toca FC which is in clinical development. All of our product candidates, including Toca 511 & Toca FC, will require additional clinical and nonclinical development, regulatory review and approval in one or more jurisdictions, substantial investment, access to sufficient pre-commercial and commercial manufacturing capacity and significant marketing efforts before we can generate any revenue from product sales. In addition, because Toca 511 & Toca FC is our most advanced product candidate, and because all of our other future product candidates will likely be based on similar technology, if Toca 511 & Toca FC encounters safety or efficacy problems, developmental delays, regulatory issues or other problems, our development plans and business for our other product candidates would be significantly harmed.

The FDA regulatory approval process is lengthy and time-consuming, and we may experience significant delays in the clinical development and regulatory approval of our product candidates. If we are ultimately unable to obtain regulatory approval for our product candidates, our business will be substantially harmed.

The time required to obtain approval by the FDA and comparable foreign authorities is unpredictable but typically takes many years following the commencement of clinical trials and depends upon numerous factors, including the substantial discretion of the regulatory authorities. In addition, approval policies, regulations or the type and amount of clinical data necessary to gain approval may change during the course of a product candidate's clinical development and may vary among jurisdictions. We have not obtained regulatory approval for any product candidate and it is possible that none of our existing product candidates or any product candidates we may seek to develop in the future will ever obtain regulatory approval.

We have not previously submitted a biologics license application, or BLA, to the FDA, or similar approval filings to comparable foreign authorities. A BLA must include extensive preclinical and clinical data and supporting information to establish the product candidate's safety, purity and potency for each desired indication. The BLA must also include significant information regarding the chemistry, manufacturing and controls for the product. Clinical testing is expensive, time-consuming and uncertain as to outcome. We have experienced in the past delays in the commencement and completion of our clinical trials. We cannot guarantee that any clinical trials will be conducted as planned or completed on schedule, if at all. A failure of one or more clinical trials can occur at any stage of testing. In addition to challenges related to patient enrollment, other events that may prevent successful or timely completion of clinical development include:

- the availability of financial resources to commence and complete our planned clinical trials;
- delays in reaching a consensus with clinical investigators on study design;
- delays in reaching a consensus with regulatory agencies on study design or approval from regulatory authorities to commence a trial;
- reaching agreement on acceptable terms with prospective clinical trial sites, the terms of which can be subject to extensive negotiation and may vary significantly among different clinical trial sites;
- delays in obtaining required IRB and/or biologic safety committee approval at each clinical trial site;
- imposition of a clinical hold by regulatory agencies, after an inspection of our clinical trial operations or study sites, or otherwise;
- failure by our CROs, other third parties or us to adhere to clinical trial requirements;
- failure to perform in accordance with the FDA's good clinical practices, or GCP, or applicable regulatory guidelines in other countries;
- failure to adequately acquire, preserve and quality assure clinical trial data;
- delays in the testing, validation, manufacturing and delivery of our product candidates to the clinical sites;
- inadequate shipping or storage of our products, resulting in loss of activity;
- delays in having patients complete participation in a study or return for post-treatment follow-up;
- clinical trial sites dropping out of a study;
- changes in legislation or regulatory requirements and guidance that require amending or submitting new clinical protocols; and
- technical equipment and/or operating room supply limitations at a clinical trial site.

We could also encounter delays if physicians encounter unresolved ethical issues associated with enrolling patients in clinical trials of our product candidates in lieu of prescribing existing treatments that have established safety and efficacy profiles. Further, a clinical trial may be suspended or terminated by us, the IRBs for the institutions in which such clinical trials are being conducted, the Data Safety Monitoring Committee for such clinical trial, the FDA or other regulatory authorities due to a number of factors, including failure to conduct the clinical trial in accordance with regulatory requirements or our clinical protocols, inspection of the clinical trial operations or clinical trial site by the FDA or other regulatory authorities resulting in the imposition of a clinical hold, unforeseen safety issues or adverse side effects, failure to demonstrate a benefit from using a product candidate, changes in governmental regulations or administrative actions or lack of adequate funding to continue the clinical trial. If we experience termination of, or delays in the completion of, any clinical trial of our product candidates, the commercial prospects for our product candidates will be harmed, and our ability to generate product revenue will be delayed. In addition, any delays in completing our clinical trials will increase our costs, slow down our product development and approval process and jeopardize our ability to commence product sales and generate revenue.

Any inability to successfully complete preclinical and clinical development could result in additional costs to us or impair our ability to generate revenues from product sales, regulatory and commercialization milestones and royalties. In addition, if we make manufacturing or formulation changes to our product candidates, we may need to conduct additional studies to bridge our modified product candidates to earlier versions. Clinical trial delays could also shorten any periods during which we may have patent protection rights to commercialize our product candidates or allow our competitors to bring products into clinical trials or to market before we do, which could impair our ability to successfully commercialize our product candidates and may harm our business and results of operations.

Our clinical trials may fail to demonstrate safety and efficacy and any of our product candidates could be associated with undesirable side effects or other properties, which would prevent or delay regulatory approval and commercialization.

Before obtaining marketing approval from regulatory authorities for the sale of our product candidates, we or our strategic partner must conduct extensive clinical trials to demonstrate the safety and efficacy of the product candidates in humans. Failure can occur at any time during a clinical trial process. The results of preclinical studies and early clinical trials of our product candidates may not be predictive of the results of later-stage clinical trials. There is typically an extremely high rate of attrition from the failure of product candidates proceeding through clinical trials. Product candidates in later stages of clinical trials may fail to show the desired safety and efficacy profile despite having progressed through preclinical testing and initial clinical trials. Most product candidates that commence clinical trials are never approved as products.

In addition, from time to time, we may publish interim, "top-line," initial, or preliminary data from our clinical studies. Interim data from clinical trials are subject to the risk that one or more of the clinical outcomes may materially change as patient enrollment continues and more patient data becomes available. Preliminary, initial, or "top-line" data also remain subject to audit and verification procedures that may result in the final data being materially different from the preliminary data we previously published. As a result, interim, "top-line", initial, and preliminary data should be viewed with caution until the final data are available. Adverse changes between preliminary, initial, "top-line" or interim data and final data could significantly harm our business prospects. Patients treated with our product candidates may also be undergoing surgical, radiation and chemotherapy treatments, which can cause side effects or adverse events that are unrelated to our product candidate, but may still impact the success of our clinical trials. Additionally, our product candidates could potentially cause other adverse events that have not yet been predicted. The inclusion of critically ill patients in our or our partner's clinical trials may result in deaths or other adverse medical events due to other therapies or medications that such patients may be using or due to the gravity of such patients' illnesses. Patients who will be administered Toca 511 & Toca FC in the high grade glioma, or HGG, clinical trials are seriously or terminally ill and some of them may have immune impairment related to their treatment with temozolomide and dexamethasone. It is expected that some of the patients will die or experience major clinical events such as strokes, hydrocephalus, infections, brain swelling and pulmonary emboli either during the course of our or our partner's clinical trials or after such trials, which has occurred in the past. In some patients with evidence of drug activity from Toca 511 & Toca FC, new lesions have been observed, some of which continue to grow even with continued Toca FC treatment.

Further, the design of our ongoing Phase 3 clinical trial of Toca 511 & Toca FC was based in part on survival data from similar patients in published trials. The prognosis, unrelated to our treatment, for our patients could be better than for patients in these prior trials, due to improvements in clinical practice, other experimental trials or underappreciated differences in entry criteria. In addition, the clinical or regulatory opinion on what constitutes the standard of care that we have used as the basis for the control arm in this clinical trial may change before we submit the BLA for Toca 511 & Toca FC, if the clinical trial is successful.

It is possible that our retroviral replicating vector, or RRV, product candidates will spread to healthy tissues and result in unknown side effects, and that any anticipated or unanticipated side effects may occur at doses required to achieve clinically relevant efficacy, which could prohibit or delay commercialization of our product candidates. Alternatively, our RRV product candidates might not spread rapidly enough through the tumor or transfer sufficient genetic material to the tumor to demonstrate efficacy sufficient for regulatory approval. In preclinical studies in rodent models, we observed that our vectors do not initially infect tumors in some locations as well as they infect tumors in other locations, which may limit treatment with our future product candidates to a limited number of cancer locations. Further, it is possible that the RRV might not spread fast enough through the brain cancer to have a beneficial effect or that the virus might not be able to reach certain parts of the tumor due to prior surgical removal of contiguous cancer tissue or from scarring resulting from surgery, chemotherapy, radiation or spontaneous tumor necrosis (cell death) or due to mechanical limitations such as the inability to insert the needle accurately into tissue bearing the tumor; the inability to push enough RRV volume into a tumo; the rapid diffusion of RRV from the injection site due to high intratumor pressure or due to the communication with the ventricular space, external cerebral spinal fluid or the entry into veins; or the inability to insert the needle into the tumor without damaging vital brain structures. It is possible that the cancers which we seek to treat with our product candidates will be or become resistant to infection with the virus or become resistant to the 5-FU (5-fluorouracil) produced from Toca FC, due to mutation within the cancer cells genes or due to mutation of Toca 511, including loss of the therapeutic gene, cytosine deaminase.

If the results of our or our partner's clinical trials are inconclusive or if there are safety concerns or adverse events associated with our product candidates, we may:

- be delayed in obtaining marketing approval for our product candidates, if at all;
- obtain approval for indications or patient populations that are not as broad as intended or desired;
- obtain approval with labeling that includes significant use or distribution restrictions or safety warnings;
- be subject to changes with the way the product is administered;
- be required to perform additional clinical trials to support approval or be subject to additional post-marketing testing requirements;
- have regulatory authorities withdraw their approval of the product or impose restrictions on its distribution in the form of a modified Risk Evaluation and Mitigation Strategy, or REMS;
- be subject to product liability or other litigation claims; or
- experience damage to our reputation.

In third-party clinical trials involving other viral vectors for gene therapy, some patients experienced serious adverse events, including the development of leukemia due to vector-related insertional oncogenesis and death. If our vectors demonstrate a similar effect, we may be required to halt or delay clinical development of our product candidates.

Existing data on the safety and efficacy of gene therapy is very limited and sometimes include historically poor clinical efficacy of previous non-replicating gene therapy products. In addition, there have been publicized safety issues associated with previous gene therapy products in third-party clinical trials, including patient deaths. The results of preclinical and clinical trials performed for our product candidates do not definitively predict safety or efficacy in humans. Possible serious side effects of other viral vector-based gene therapy therapies in general include uncontrolled viral infections and the development of cancer, particularly lymphoma or leukemia.

A significant risk in any gene therapy product based on viral vectors that integrate into the host genome at measurable frequencies is that the vector will insert near cancer-linked oncogenes leading to uncontrolled clonal proliferation of mature cancer cells in the patient. A potential clinical concern for gene therapy using retroviral vectors has been the possibility of insertional mutagenesis by the vectors, leading to malignant transformation of transduced cells (i.e., cancer). Because our replicating retroviruses produce viral antigens, these foreign proteins could serve as a target for immune activation against virally-infected cells and inflammation, which is not a feature of non-replicating retroviral vectors. In addition, we have not, and do not plan to, treat patients with severe immunodeficiency with our product candidates. Further, with our lead product candidate, Toca FC kills the virally-infected cells and presents the antigens. We believe that we have not observed oncogenesis in the patients treated in our clinical trials to date for these reasons. Our future product candidates are also designed to activate the immune system against virally-infected cells.

It is possible Toca 511 may spread to non-tumor tissue. We have detected transient and low levels of viral sequences in the saliva of several patients. The risk of insertional mutagenesis or oncogenesis remains a significant concern for gene therapy, and we cannot provide any assurance that it will not occur in any of our current, planned or future clinical trials. There is also the potential risk of delayed adverse events following exposure to gene therapy products due to persistent biological activity of the genetic material or other components of products used to carry the genetic material. If any such adverse events occur, further advancement of our clinical trials could be halted or delayed, which would have a material adverse effect on our business and operations.

We may not be successful in our efforts to identify or discover additional product candidates from our gene therapy platform.

The success of our business depends primarily upon our ability to identify, develop and commercialize products based on our gene therapy platform. Although our Toca 511 & Toca FC product candidate is currently in clinical development, our research programs may fail to identify other potential product candidates for clinical development. Our research methodology may be unsuccessful in identifying potential product candidates, or our potential product candidates may be shown to have harmful side effects or may have other characteristics that may make the products unmarketable or unlikely to receive marketing approval. If any of these events occur, we may be forced to abandon our development efforts for a program or programs, which would have a material adverse effect on our business and could potentially cause us to cease operations.

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

We rely on CROs and clinical trial sites to ensure our clinical trials are conducted properly and on time. While we have agreements governing their activities, we may have limited influence over their actual performance. We control only certain aspects of our CROs' activities. Nevertheless, we are responsible for ensuring that each of our clinical trials is conducted in accordance with the applicable protocol, legal, regulatory and scientific standards, and our reliance on the CROs does not relieve us of our regulatory responsibilities.

We and our CROs are required to comply with the GCPs for conducting, recording, auditing and reporting the results of clinical trials to assure that the data and reported results are credible and accurate and that the rights, integrity and confidentiality of clinical trial participants are protected. The FDA enforces these GCPs through periodic inspections of study sponsors, principal investigators and clinical trial sites. If we or our CROs fail to comply with applicable GCPs, the clinical data generated in our future clinical trials may be deemed unreliable, and the FDA may require us to perform additional clinical trials before approving any marketing applications. Upon inspection, the FDA may determine that our clinical trials did not comply with GCPs. In addition, our ongoing and future clinical trials will require a sufficient number of test subjects to evaluate the safety and effectiveness of our product candidates. Accordingly, if our CROs fail to comply with these regulations or fail to recruit a sufficient number of patients, we may be required to repeat such clinical trials, which would delay the regulatory approval process.

Our CROs are not our employees, and we are not able to directly monitor whether or not they devote sufficient time and resources to our clinical and nonclinical programs. These CROs may also have relationships with other commercial entities, including our competitors, for whom they may also be conducting clinical trials or other drug development activities that could harm our competitive position. If our CROs do not successfully carry out their contractual duties or obligations, fail to meet expected deadlines, or if the quality or accuracy of the clinical data they obtain is compromised due to their failure to adhere to our clinical protocols or regulatory requirements, or for any other reasons, our clinical trials may be extended, delayed or terminated, and we may not be able to obtain regulatory approval for or successfully commercialize our product candidates. As a result, our financial results and the commercial prospects for our product candidates would be harmed, our costs could increase and our ability to generate revenues could be delayed.

We may have difficulty enrolling patients in our clinical trials, which could delay or prevent development of our product candidates.

Identifying and qualifying patients to participate in clinical trials of our product candidates is critical to our success. The timing of our clinical trials depends on the speed at which we can recruit patients to participate in testing our product candidates. We have experienced delays in some of our clinical trials in the past due to difficulties with enrollment and we may experience similar delays in the future. If patients are unwilling to participate in our clinical trials because of negative publicity from adverse events in the industry or in the trials for other third party product candidates, or for other reasons, including competitive clinical trials for similar patient populations, the timeline for recruiting patients, conducting studies and obtaining regulatory approval of potential products may be delayed. These delays could result in increased costs, delays in advancing our product development, delays in testing the effectiveness of our technology or termination of the clinical trials altogether.

We or our clinical trial sites may not be able to identify, recruit and enroll a sufficient number of patients, or those with the required or desired characteristics in a clinical trial, to complete our clinical trials in a timely manner. Patient enrollment is affected by factors including:

- severity of the disease under investigation;
- design of the clinical trial protocol, including the fact that certain of our clinical trials are randomized to current treatments;
- size of the patient population;
- eligibility criteria for the clinical trial in question;
- perceived risks and benefits of the product candidate under study;
- general level of excitement for the treatment approach;
- comments on social media;
- proximity and availability of clinical trial sites for prospective patients;
- availability of competing therapies and clinical trials;
- efforts to facilitate timely enrollment in clinical trials;
- patient referral practices of physicians; and
- ability to monitor patients adequately during and after treatment.

The eligibility criteria of our clinical trials will limit the pool of available trial participants. Additionally, the process of finding and diagnosing patients may prove costly. Finally, our treatment necessitates that the patient be near one of our clinical trial sites, since periodic follow-up visits at the clinical trial site are contemplated in the protocols.

We currently plan to seek initial marketing approval in the United States and subsequently other pharmaceutical markets. We may not be able to initiate or continue clinical trials if we cannot enroll a sufficient number of eligible patients to participate in the clinical trials required by the FDA, the EMA or other regulatory agencies. Our ability to successfully initiate, enroll and complete a clinical trial in any foreign country is subject to numerous risks unique to conducting business in foreign countries, including:

- difficulty in establishing or managing relationships with contract research organizations, or CROs, and physicians;
- different standards for the conduct of clinical trials;
- our inability to locate qualified local consultants, physicians and partners; and
- the potential burden of complying with a variety of foreign laws, medical standards and regulatory requirements, including the regulation of pharmaceutical and biotechnology products and treatments.

If we have difficulty enrolling a sufficient number of patients to conduct our clinical trials as planned, we may need to delay, limit or terminate ongoing or planned clinical trials, any of which would have an adverse effect on our business.

Our reliance on third parties may require us to share our trade secrets, which increases the possibility that a competitor will discover them or that our trade secrets will be misappropriated or disclosed.

Because we rely on third parties to manufacture our vectors and our product candidates, and because we collaborate with various organizations and academic institutions on the advancement of our gene therapy platform, we must, at times, share trade secrets with them. We seek to protect our proprietary technology in part by entering into confidentiality agreements and, if applicable, material transfer agreements, collaborative research agreements, consulting agreements or other similar agreements with our manufacturers, collaborators, advisors, employees and consultants prior to beginning research or disclosing proprietary information. These agreements typically limit the rights of the third parties to use or disclose our confidential information, such as trade secrets. Despite the contractual provisions employed when working with third parties, the need to share trade secrets and other confidential information increases the risk that such trade secrets become known by our competitors, are inadvertently incorporated into the technology of others, are used inappropriately to create new inventions or are disclosed or used in violation of these agreements. Given that our proprietary position is based, in part, on our know-how and trade secrets, a competitor's discovery of our trade secrets or other unauthorized use or disclosure would impair our competitive position and may have a material adverse effect on our business.

In addition, these agreements typically restrict the ability of our collaborators, advisors, employees and consultants to publish data potentially relating to our trade secrets. Our academic collaborators typically have rights to publish data, provided that we are notified in advance and may delay publication for a specified time in order to secure our intellectual property rights arising from the collaboration. In other cases, publication rights are controlled exclusively by us, although in some cases we may share these rights with other parties. We also conduct joint research and development programs that may require us to share trade secrets under the terms of our research and development partnerships or similar agreements. Despite our efforts to protect our trade secrets, our competitors may discover our trade secrets through breach of these agreements, independent development or publication of information including our trade secrets in cases where we do not have proprietary or otherwise protected rights at the time of publication. A competitor's discovery of our trade secrets may impair our competitive position and have an adverse impact on our business.

We are dependent on ApolloBio to develop and commercialize Toca 511 & Toca FC within the greater China region, including mainland China, Hong Kong, Macao and Taiwan. Failure of ApolloBio or any other third parties to successfully develop and commercialize Toca 511 & Toca FC in the applicable jurisdictions could have a material adverse effect on our business.

We have granted ApolloBio an exclusive license to develop and commercialize Toca 511 & Toca FC within the greater China region, including mainland China, Hong Kong, Macao and Taiwan. We have limited contractual rights to force ApolloBio to invest significantly in the development and commercialization of Toca 511 & Toca FC.

In the event that ApolloBio or any other third party with any future development and commercialization rights to any of our product candidates fails to adequately develop and commercialize those product candidates because they lack adequate financial or other resources, decide to focus on other initiatives or otherwise, our ability to successfully develop and commercialize our product candidates in the applicable jurisdictions would be limited, which would adversely affect our business, financial condition, results of operations and prospects. In addition, our license agreement with ApolloBio may be terminated by either party upon a material breach by the other party that remains uncured following 60 days (or, with respect to any payment breach, 10 days) after the date of written notice of such breach, may be terminated by ApolloBio at any time by providing us 90 days' prior written notice and may be terminated by us upon written notice to ApolloBio under specified circumstances if ApolloBio challenges the licensed patent rights. If we or ApolloBio terminate our license agreement, our ability to develop and commercialize Toca 511 & Toca FC within the greater China region, including mainland China, Hong Kong, Macao and Taiwan, would be materially harmed.

Any adverse developments that occur during any clinical trials conducted by ApolloBio may affect our ability to obtain regulatory approval or commercialize Toca 511 & Toca FC.

ApolloBio retains the rights to develop and commercialize Toca 511 & Toca FC in the greater China region, including mainland China, Hong Kong, Macao and Taiwan. If serious adverse events occur during any clinical trials ApolloBio decides to conduct with respect to Toca 511 & Toca FC, the FDA and other regulatory authorities may delay, limit or deny approval of Toca 511 & Toca FC or require us to conduct additional clinical trials as a condition to marketing approval, which would increase our costs. If we receive FDA approval for Toca 511 & Toca FC and a new and serious safety issue is identified in connection with clinical trials conducted by ApolloBio, the FDA and other regulatory authorities may withdraw their approval of the product or otherwise restrict our ability to market and sell our product. In addition, treating physicians may be less willing to administer our product due to concerns over such adverse events, which would limit our ability to commercialize Toca 511 & Toca FC. ApolloBio is not currently conducting any clinical trials of Toca 511 & Toca FC.

We face intense competition and rapid technological change and the possibility that our competitors may develop therapies that are more advanced or effective than ours, which may adversely affect our financial condition and our ability to successfully commercialize our product candidates.

We are engaged in developing gene therapies and cancer immunotherapies, which are rapidly evolving and fiercely competitive fields. A wide variety of institutions in the United States and internationally, including major multinational pharmaceutical companies, specialty biotechnology companies, academic research departments and public and private institutions, are actively developing potentially competitive technology and products. We face substantial competition from biotechnology and pharmaceutical companies developing products in immunotherapy and our initial proposed indication. Our competitors generally fall into the following categories: companies developing checkpoint inhibitors; companies developing immunotherapies; companies aimed at stimulating immune responses; companies developing CAR and TCR T cells; companies developing oncolytic virus-based technology; and companies with a focus on HGG.

Many of our competitors have substantially greater financial, technical and other resources, such as larger research and development staff and experienced marketing and manufacturing organizations. Accordingly, our competitors may be more successful than us in obtaining approval for treatments and achieving widespread market acceptance, rendering our treatments obsolete or non-competitive. These companies also compete with us in recruiting and retaining qualified scientific and management personnel, establishing clinical trial sites and patient registration for clinical trials and acquiring technologies complementary to, or necessary for, our programs. Smaller or early-stage companies may also prove to be significant competitors, particularly through collaborative arrangements with large and established companies.

If these competitors develop and commercialize more effective, safer or less toxic products than us or if they obtain regulatory approval before us in key geographies, our commercial opportunities could be substantially limited. In addition, adverse clinical outcomes or similar events at gene therapy companies in the past have adversely affected other companies in this field and could also do so in the future at our company.

Even if we obtain regulatory approval of our product candidates, the products may not gain market acceptance among physicians, patients, hospitals, cancer treatment centers, third-party payors and others in the medical community.

Ethical, social and legal concerns about gene therapy and genetic research could result in additional regulations restricting or prohibiting the products and processes we may use. Even with the requisite approvals, the commercial success of our product candidates will depend in part on the medical community, patients, and third-party payors accepting gene therapy products in general, and our product candidates in particular, as medically useful, cost-effective and safe. Any product that we bring to the market may not gain market acceptance by physicians, patients, third-party payors and others in the medical community. If these products do not achieve an adequate level of acceptance, we may not generate significant product revenue and may not become profitable. The degree of market acceptance of these product candidates, if approved for commercial sale, will depend on a number of factors, including:

- the clinical indications for which our product candidates are approved;
- physicians, hospitals, cancer treatment centers and patients considering our product candidates as a safe and effective treatment;
- the potential and perceived advantages of our product candidates over alternative treatments;
- the prevalence and severity of any side effects;
- product labeling or product insert requirements of the FDA or other regulatory authorities;
- limitations or warnings contained in the labeling approved by the FDA;
- the timing of market introduction of our product candidates as well as competitive products;
- the pricing and cost-effectiveness of our product candidates as well as the cost of treatment in relation to alternative treatments;
- the availability of favorable coverage and adequate reimbursement by third-party payors and government authorities;
- the willingness of patients to pay out-of-pocket in the absence of coverage or adequate reimbursement by third-party payors, including government authorities;
- the willingness, ability and availability of healthcare providers that can comply with the transportation, handling, and temperature-controlled storage requirements associated with our product candidates;
- relative convenience and ease of administration, including as compared to alternative treatments and competitive therapies; and
- the effectiveness of our sales and marketing efforts.

Even if a potential product displays a favorable efficacy and safety profile in preclinical and clinical trials, market acceptance of the product will not be known until after it is launched. Our efforts to educate the medical community and third-party payors on the benefits of the product candidates may require significant resources and may never be successful. Such efforts to educate the marketplace may require more resources than are required by the conventional technologies marketed by our competitors and may be restricted by the allowed label.

We are highly dependent on our key personnel, and if we are not successful in attracting and retaining highly qualified personnel, we may not be able to successfully implement our business strategy.

Our ability to compete in the highly competitive biotechnology and pharmaceutical industries depends upon our ability to attract and retain highly qualified managerial, scientific and medical personnel. We are highly dependent on our management, scientific and medical personnel. The loss of the services of any of our executive officers, other key employees and other scientific and medical advisors, and our inability to find suitable replacements, could result in delays in product development and harm our business.

To induce valuable employees to remain at our company, in addition to salary and cash incentives, we have provided stock options that vest over time. The value to employees of stock options that vest over time may be significantly affected by movements in our stock price that are beyond our control and may at any time be insufficient to counteract more lucrative offers from other companies. Despite our efforts to retain them, valuable employees and members of our management, scientific and development teams may terminate their employment with us at any time, with or without notice. We do not maintain "key man" insurance policies on the lives of any of our executive officers or other employees. Our success also depends on our ability to continue to attract, retain and motivate highly skilled scientific and medical personnel.

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

As of December 31, 2018, we had 79 full-time employees. As our development and commercialization plans and strategies develop, and as we continue operating as a public company, we expect to need additional managerial, operational, sales, marketing, financial and other personnel. Future growth would impose significant added responsibilities on members of management. There are a small number of individuals with experience in gene therapy and clinicians who have successfully developed drugs and the competition for such individuals is high. Our future financial performance and our ability to commercialize our product candidates will depend, in part, on our ability to effectively manage any future growth, and our management may also have to divert a disproportionate amount of its attention away from day-to-day activities in order to devote a substantial amount of time to managing these growth activities. We currently rely, and for the foreseeable future will continue to rely on certain independent organizations, advisors and consultants to provide certain services, including substantially all aspects of regulatory approval, clinical management and manufacturing. There can be no assurance that the services of independent organizations, advisors and consultants will continue to be available to us on a timely basis when needed or that we can find qualified replacements. In addition, if we are unable to effectively manage our outsourced activities or if the quality or accuracy of the services provided by consultants is compromised for any reason, our clinical trials may be extended, delayed or terminated, and we may not be able to obtain regulatory approval of our product candidates or otherwise advance our business. There can be no assurance that we will be able to manage our existing consultants or find other competent outside contractors and consultants on economically reasonable terms, or at all.

If we are not able to effectively expand our organization by hiring new employees and expanding our groups of consultants and contractors, we may not be able to successfully implement the tasks necessary to further develop and commercialize our product candidates and, accordingly, may not achieve our research, development and commercialization goals.

We may use our financial and human resources to pursue a particular research program or product candidate and fail to capitalize on programs or product candidates that may be more profitable or for which there is a greater likelihood of success.

Because we have limited resources, we may forego or delay pursuit of opportunities with certain programs or product candidates or for indications that later prove to have greater commercial potential. Our resource allocation decisions may cause us to fail to capitalize on viable commercial products or profitable market opportunities. Our spending on current and future research and development programs for product candidates may not yield any commercially viable products. If we do not accurately evaluate the commercial potential or target market for a particular product candidate, we may relinquish valuable rights to that product candidate through strategic collaboration, licensing or other royalty arrangements in cases in which it would have been more advantageous for us to retain sole development and commercialization rights to such product candidate, or we may allocate internal resources to a product candidate in a therapeutic area in which it would have been more advantageous to enter into a partnering arrangement.

We currently have a limited marketing and sales organization. If we are unable to expand our marketing and sales capabilities or enter into agreements with third parties to market and sell our product candidates, we may not be able to generate product revenue.

We currently have limited sales, marketing and distribution capabilities. At the appropriate time, we plan to further build our commercial infrastructure targeting oncologists, neuro-oncologists and neurosurgeons and related clinicians and health care workers in leading and regional cancer centers in the United States, which will require significant capital expenditures, management resources and time. ApolloBio retains the rights to develop and commercialize Toca 511 & Toca FC in the greater China region, including mainland China, Hong Kong, Macao and Taiwan. We may build our own commercial infrastructure in other territories or consider additional opportunities to enter into out-licensing or co-promotion agreements with other pharmaceutical or biotechnology companies to develop and/or commercialize our product candidates outside the United States. We will have to compete with other pharmaceutical and biotechnology companies to recruit, hire, train and retain marketing and sales personnel.

If we are unable or decide not to expand our internal sales, marketing and distribution capabilities, we will pursue collaborative arrangements regarding the sales and marketing of our products, however, there can be no assurance that we will be able to establish or maintain such collaborative arrangements, or if we are able to do so, that they will have effective sales forces. Any revenue we receive will depend upon the efforts of such third parties, which may not be successful. We may have little or no control over the marketing and sales efforts of such third parties, and our revenue from product sales may be lower than if we had commercialized our product candidates ourselves. We also face competition in our search for third parties to assist us with the sales and marketing efforts of our product candidates.

There can be no assurance that we will be able to develop in-house sales and distribution capabilities or establish or maintain relationships with third-party collaborators to commercialize any product in the United States or elsewhere.

A variety of risks associated with marketing our product candidates internationally could materially adversely affect our business.

We plan to seek regulatory approval of our product candidates outside of the United States and, accordingly, we expect that we will be subject to additional risks related to operating in foreign countries if we obtain the necessary approvals, including:

- differing regulatory requirements and reimbursement regimes in foreign countries;
- unexpected changes in tariffs, trade barriers, price and exchange controls and other regulatory requirements;
- economic weakness, including inflation, or political instability in particular foreign economies and markets;
- compliance with tax, employment, immigration and labor laws for employees living or traveling abroad;
- foreign taxes, including withholding of payroll taxes;
- foreign currency fluctuations, which could result in increased operating expenses and reduced revenue, and other obligations incident to doing business in another country;
- difficulties staffing and managing foreign operations;
- workforce uncertainty in countries where labor unrest is more common than in the United States;
- potential liability under the Foreign Corrupt Practices Act of 1977 or comparable foreign regulations;
- challenges enforcing our contractual and intellectual property rights, especially in those foreign countries that do not respect and protect intellectual property rights to the same extent as the United States;
- production shortages resulting from any events affecting raw material supply or manufacturing capabilities abroad; and
- business interruptions resulting from geo-political actions, including war and terrorism.

These and other risks associated with our international operations may materially adversely affect our ability to attain or maintain profitable operations.

The terms of our Loan Agreement place restrictions on our operating and financial flexibility.

In May 2018, we entered into a Loan Agreement with Oxford Finance LLC and Silicon Valley Bank, as amended in August 2018, which is secured by substantially all of our assets other than our intellectual property (except rights to payment from the sale, licensing or disposition of such intellectual property). We borrowed $26.5 million upon execution of the Loan Agreement. Approximately $8.6 million of the proceeds received was used to repay the outstanding principal, interest and final payment fees owed under our prior loan and security agreement.

The Loan Agreement includes affirmative and negative covenants applicable to us and any subsidiaries we create in the future. The affirmative covenants include, among others, covenants requiring us to maintain our legal existence and governmental approvals, deliver certain financial reports, maintain insurance coverage, and subject all of our deposit accounts, securities accounts, commodity accounts or any other bank accounts, to a control agreement in favor of Oxford Finance LLC. The negative covenants include, among others, restrictions on us transferring collateral, incurring additional indebtedness, engaging in mergers or acquisitions, paying dividends in cash or making other distributions, making investments, creating liens, selling assets, and suffering a change in control, in each case subject to certain exceptions.

The Loan Agreement also includes events of default, the occurrence and continuation of which provide Oxford Finance LLC, as collateral agent, with the right to exercise remedies against us and the collateral securing the loans under the Loan Agreement, including foreclosure against our properties securing the Loan Agreement, including our cash, potentially requiring us to renegotiate our agreement on terms less favorable to us or to immediately cease operations. These events of default include, among other things, our failure to pay any amounts due under the Loan Agreement, a breach of covenants under the loan and security agreement, our

insolvency, impairment in the perfection or priority of each lender's security interest in the collateral, the occurrence of any default under certain other indebtedness in an amount greater than $250,000, our failure to obtain or maintain material governmental approvals, and a final judgment against us of at least $250,000. Further, if we are liquidated, the lender's right to repayment would be senior to the rights of the holders of our common stock to receive any proceeds from the liquidation. The lenders could declare a default upon the occurrence of any event that they interpret as a material adverse change as defined under the Loan Agreement, thereby requiring us to repay the loan immediately or to attempt to reverse the declaration of default through negotiation or litigation. Any declaration by the lenders of an event of default could significantly harm our business and prospects and could cause the price of our common stock to decline.

If product liability lawsuits are brought against us, we may incur substantial liabilities and may be required to limit commercialization of our product candidates.

We face an inherent risk of product liability as a result of the clinical testing of our product candidates and will face an even greater risk if we commercialize any products. For example, we may be sued if our product candidates cause or are perceived to cause injury or are found to be otherwise unsuitable during clinical testing, manufacturing, marketing or sale. Any such product liability claims may include allegations of defects in manufacturing, defects in design, a failure to warn of dangers inherent in the product, negligence, strict liability or a breach of warranties. Claims could also be asserted under state consumer protection acts. If we cannot successfully defend ourselves against product liability claims, we may incur substantial liabilities or be required to limit commercialization of our product candidates. Even successful defense would require significant financial and management resources. Regardless of the merits or eventual outcome, liability claims may result in:

- decreased demand for our product candidates;
- injury to our reputation;
- withdrawal of clinical trial participants;
- initiation of investigations by regulators;
- costs to defend the related litigation;
- a diversion of management's time and our resources;
- substantial monetary awards to clinical trial participants or patients;
- product recalls, withdrawals or labeling, marketing or promotional restrictions;
- exhaustion of any available insurance and our capital resources;
- loss of revenue;
- the inability to commercialize any product candidate; and
- a decline in our share price.

Our inability to obtain sufficient product liability insurance at an acceptable cost to protect against potential product liability claims could prevent or inhibit the commercialization of any products we develop, alone or with corporate collaborators. We currently carry $5 million of product liability insurance covering our clinical trials. Although we maintain such insurance, our insurance policies may have various exclusions, and we may be subject to a product liability claim for which we have no coverage. We may have to pay any amounts awarded by a court or negotiated in a settlement that exceed our coverage limitations or that are not covered by our insurance, and we may not have, or be able to obtain, sufficient capital to pay such amounts. Even if our agreements with any future corporate collaborators entitle us to indemnification against losses, such indemnification may not be available or adequate should any claim arise.

Negative public opinion and increased regulatory scrutiny of gene therapy and genetic research may damage public perception of our product candidates or adversely affect our ability to conduct our business or obtain regulatory approvals for our product candidates.

Public perception may be influenced by claims that gene therapy is unsafe, and gene therapy may not gain the acceptance of the public or the medical community. In particular, our success will depend upon physicians specializing in the treatment of those diseases that our product candidates target prescribing treatments that involve the use of our product candidates in lieu of, or in addition to, existing treatments with which they are already familiar with and for which greater clinical data may be available. More restrictive government regulations or negative public opinion would have a negative effect on our business or financial condition and may delay or impair the development and commercialization of our product candidates or demand for any products we may develop. Adverse events in our clinical trials, even if not ultimately attributable to our product candidates, and the resulting publicity could lead to increased governmental regulation, unfavorable public perception, potential regulatory delays in the testing or approval of our potential product candidates, stricter labeling requirements for those product candidates that are approved and a decrease in demand for any such product candidates. Concern about environmental spread of our product, whether real or anticipated, may hinder the commercialization of our products.

Our internal computer systems, or those used by our CROs, SaaS providers, contractors or consultants, may fail or suffer security breaches.

Despite the implementation of security measures, our internal computer systems and those of our CROs, SaaS providers, contractors and consultants are vulnerable to damage from computer viruses and unauthorized access. While we have not experienced any such material system failure or security breach to date, if such an event were to occur and cause interruptions in our operations, it could result in a material disruption of our development programs and our business operations. For example, the loss of clinical trial data from completed or future clinical trials could result in delays in our regulatory approval efforts and significantly increase our costs to recover or reproduce the data. To the extent that any disruption or security breach were to result in a loss of, or damage to, our data or applications, or inappropriate disclosure of confidential or proprietary information, we could incur liability, and the further development and commercialization of our product candidates could be delayed.

Our business could be negatively impacted by cyber security threats.

In the ordinary course of our business, we use our data centers and our networks to store and access our proprietary business information. We face various cyber security threats, including cyber security attacks to our information technology infrastructure and attempts by others to gain access to our proprietary or sensitive information. The procedures and controls we use to monitor these threats and mitigate our exposure may not be sufficient to prevent cyber security incidents. The result of these incidents could include disrupted operations, lost opportunities, misstated financial data, liability for stolen assets or information, increased costs arising from the implementation of additional security protective measures, litigation and reputational damage. Any remedial costs or other liabilities related to cyber security incidents may not be fully insured or indemnified by other means.

Business disruptions could seriously harm our future revenue and financial condition and increase our costs and expenses.

Our operations, and those of our CROs, contractors and consultants, could be subject to power shortages, telecommunications failures, wildfires, water shortages, floods, earthquakes, hurricanes, typhoons, fires, extreme weather conditions, medical epidemics and other natural or man-made disasters or business interruptions for which we are predominantly self-insured. The occurrence of any of these business disruptions could seriously harm our operations and financial condition and increase our costs and expenses. Our ability to obtain clinical supplies of our product candidates could be disrupted if the operations of our contract manufacturers or cell line storage facilities are affected by a man-made or natural disaster or other business interruption.

Risks related to government regulation

The FDA may disagree with our regulatory plans, and we may fail to obtain regulatory approval of our product candidates.

Following receipt of Breakthrough Therapy Designation from the FDA, we redesigned our Phase 2/3 clinical trial of Toca 511 & Toca FC for the treatment of recurrent HGG to a single Phase 3 trial design and have included the 187 patients that were previously enrolled in the Phase 2/3 trial in the total of approximately 380 patients enrolled in the redesigned trial. The interim or final analyses of this trial alone could support approval of a BLA for Toca 511 & Toca FC in the indication of recurrent HGG. However, the general approach for FDA approval of a new biologic or drug is to require dispositive data from two adequate and well-controlled Phase 3 clinical trials of the biologic or drug in the relevant patient population.

In addition, we believe that it is likely that there may be a regulatory requirement for one or more diagnostic assays to monitor treatment, especially for the presence of Toca 511 & Toca FC or their components or derivatives. We plan to meet with the FDA to discuss the development of such assays, and it is possible that the FDA may require a separate regulatory approval for such assays contemporaneously with the approval of Toca 511 & Toca FC.

Our clinical trials results may not support approval. In addition, Toca 511 & Toca FC and our other product candidates could fail to receive regulatory approval for many reasons, including the following:

- the FDA or comparable foreign regulatory authorities may disagree with the design or implementation of our clinical trials, including clinical endpoints;
- the results of clinical trials may not meet the level of statistical significance required by the FDA or comparable foreign regulatory authorities for approval;
- we may be unable to demonstrate that our product candidates' clinical and other benefits outweigh their safety risks or are better than recently produced safety or efficacy data for other products;
- we may encounter serious and unexpected adverse events during clinical trials that render our products unsafe for use in humans;
- the FDA or comparable foreign regulatory authorities may disagree with our interpretation of data from preclinical studies or clinical trials;

- the data collected from clinical trials of our product candidates may not be sufficient to the satisfaction of the FDA or comparable foreign regulatory authorities to support the submission of a BLA or other comparable submission in foreign jurisdictions or to obtain regulatory approval in the United States or elsewhere;
- the FDA or comparable foreign regulatory authorities may fail to approve our manufacturing processes and/or facilities of third-party manufacturers with which we contract for clinical and commercial supplies; and
- the approval policies or regulations of the FDA or comparable foreign regulatory authorities may significantly change in a manner rendering our clinical data insufficient for approval.

Obtaining and maintaining regulatory approval of our product candidates in one jurisdiction does not mean that we will be successful in obtaining regulatory approval of our product candidates in other jurisdictions.

Obtaining and maintaining regulatory approval of our product candidates in one jurisdiction does not guarantee that we will be able to obtain or maintain regulatory approval in any other jurisdiction, while a failure or delay in obtaining regulatory approval in one jurisdiction may have a negative effect on the regulatory approval process in others. For example, even if the FDA grants marketing approval of a product candidate, comparable regulatory authorities in foreign jurisdictions must also approve the manufacturing, marketing and promotion of the product candidate in those countries. Approval procedures vary among jurisdictions and can involve requirements and administrative review periods different from, and greater than, those in the United States, including additional preclinical studies or clinical trials. Studies and clinical trials conducted in one jurisdiction or study group may not be accepted by regulatory authorities in other jurisdictions. In many jurisdictions outside the United States, a product candidate must be approved for reimbursement before it can be approved for sale in that jurisdiction. In some cases, the price that we intend to charge for our products is also subject to approval.

We may also submit marketing applications in other countries. Regulatory authorities in jurisdictions outside of the United States have requirements for approval of product candidates with which we must comply prior to marketing in those jurisdictions. Obtaining foreign regulatory approvals and compliance with foreign regulatory requirements could result in significant delays, difficulties and costs for us and could delay or prevent the introduction of our products in certain countries. If we fail to comply with the regulatory requirements in international markets and/or receive applicable marketing approvals, our target market will be reduced and our ability to realize the full market potential of our product candidates will be harmed.

Additional time may be required to obtain regulatory approval for Toca 511 & Toca FC because it is a combination product.

We believe our Toca 511 & Toca FC product candidate is regulated as a drug/biologic combination product, which will require coordination within the FDA and similar foreign regulatory agencies for review of their biologic and drug components and potentially one or more diagnostic assays to monitor treatment. Although the FDA and similar foreign regulatory agencies have systems in place for the review and approval of combination products such as ours, we may experience delays in the development and commercialization of our product candidates due to regulatory timing constraints and uncertainties in the product development and approval process.

Even if we receive regulatory approval of our product candidates, we will be subject to ongoing regulatory obligations and continued regulatory review, which may result in significant additional expense, and we may be subject to penalties and/or withdrawal of product approval if we fail to comply with regulatory requirements or experience unanticipated problems with our product candidates.

Any regulatory approvals that we receive for our product candidates will require surveillance to monitor the safety and efficacy of the product candidate. Specifically, we believe that it is likely that there may be a regulatory requirement for one or more diagnostic assays to monitor treatment, especially for the presence of Toca 511 or Toca FC or their components or derivatives. We plan to meet with the FDA to discuss the development of such assays, and it is possible that the FDA may require a separate regulatory approval for such assays. Further, each vector containing a particular gene could be regulated as a separate biologic depending on its intended use and FDA policy. The FDA may also require a REMS, in order to approve our product candidates, which could entail requirements for a medication guide, physician communication plans or additional elements to ensure safe use, such as restricted distribution methods, patient registries and other risk minimization tools. In addition, if the FDA or a comparable foreign regulatory authority approves our product candidates, the manufacturing processes, labeling, packaging, distribution, adverse event reporting, storage, advertising, promotion, import, export and record keeping for our product candidates will be subject to extensive and ongoing regulatory requirements. These requirements include, among other things, submissions of safety and other post-marketing information and reports, registration, as well as continued compliance with cGMPs for manufacturing and GCPs for any clinical trials that we conduct post-approval. Later discovery of previously unknown problems with our product candidates, including adverse events of unanticipated severity or frequency, or with our third-party manufacturers or manufacturing processes, or failure to comply with regulatory requirements, may result in, among other things:

- restrictions on the marketing or manufacturing of our product candidates, withdrawal of the product from the market, or voluntary or mandatory product recalls;
- fines, warning letters or holds on clinical trials;

- refusal by the FDA to approve pending applications or supplements to approved applications filed by us or suspension or revocation of license approvals;
- suspension or termination of manufacturing at one or more manufacturing facilities;
- product seizure or detention, or refusal to permit the import or export of our product candidates; and
- injunctions or the imposition of civil or criminal penalties.

Moreover, the FDA strictly regulates the promotional claims that may be made about drug and biologic products. In particular, a product may not be promoted for uses that are not approved by the FDA as reflected in the product's approved labeling. The FDA and other agencies actively enforce the laws and regulations prohibiting the promotion of off-label uses, and a company that is found to have improperly promoted off-label uses may be subject to significant civil, criminal and administrative penalties.

The FDA's and other regulatory authorities' policies may change and additional government regulations may be enacted that could prevent, limit or delay regulatory approval of our product candidates. We cannot predict the likelihood, nature or extent of government regulation that may arise from future legislation or administrative action, either in the United States or abroad.

We have Orphan-Drug Designation for Toca 511 & Toca FC for the treatment of malignant glioma in addition to glioblastoma multiforme, or GBM, but we may be unable to maintain the benefits associated with Orphan-Drug Designation, including potential eligibility for any future market exclusivity.

Under the Orphan-Drug Act, the FDA may grant orphan designation to a drug or biologic intended to treat a rare disease or condition, which is defined as one occurring in a patient population of fewer than 200,000 in the United States, or a patient population greater than 200,000 in the United States for which there is no reasonable expectation that the cost of developing and making available in the United States a drug or biologic for a disease or condition will be recovered from sales in the United States for that drug or biologic. In the United States, Orphan-Drug Designation entitles a party to financial incentives such as opportunities for grant funding towards clinical trial costs, tax advantages and user-fee waivers. In addition, if a product that has Orphan-Drug Designation subsequently receives the first FDA approval for the disease for which it has such designation, the product is entitled to orphan product exclusivity, which means that the FDA may not approve any other applications to market the same biologic for the same indication for seven years, except in limited circumstances, such as a showing of clinical superiority to the product with orphan drug exclusivity or where the manufacturer is unable to assure sufficient product quantity.

Toca 511 & Toca FC has Orphan-Drug Designation in the United States for the treatment of malignant glioma in addition to GBM, and in the European Union for the treatment of glioma. We are currently developing this product candidate for the treatment of recurrent HGG, which is a subset of malignant glioma. Exclusive marketing rights in the United States may be limited if we seek approval for an indication broader than the orphan designated indication and may be lost if the FDA later determines that the request for designation was materially defective or if the manufacturer is unable to assure sufficient quantities of the product to meet the needs of patients with the rare disease or condition. Further, even if we obtain orphan drug exclusivity for a product, that exclusivity may not effectively protect the product from competition because different products with different active moieties can be approved for the same condition. Even after an orphan product is approved, the FDA can subsequently approve the same product with the same active moiety for the same condition if the FDA concludes that the later product is safer, more effective or makes a major contribution to patient care. Orphan-Drug Designation neither shortens the development time or regulatory review time of a drug or biologic nor gives the drug or biologic any advantage in the regulatory review or approval process. In addition, while we may seek orphan designation for other product candidates, we may never receive such designations.

A Fast Track Designation or Breakthrough Therapy Designation by the FDA or Priority Medicines, or PRIME, Designation by the EMA, may not actually lead to a faster development or regulatory review or approval process.

If a product candidate is intended for the treatment of a serious or life-threatening condition and demonstrates the potential to address unmet medical needs for this condition, the drug sponsor may apply for FDA Fast Track Designation. Similarly, Breakthrough Therapy Designation may be granted by the FDA, or PRIME Designation may be granted by the EMA, to product candidates for serious conditions that have preliminary clinical evidence indicating the product candidate may offer substantial improvement over available therapy. The FDA and EMA have broad discretion whether or not to grant these designations, and even if we believe a particular product candidate is eligible for these designations, we cannot assure you that the FDA or EMA would decide to grant them. We have been granted Fast Track Designation and Breakthrough Therapy Designation for our Toca 511 & Toca FC product candidate for the treatment of recurrent HGG and PRIME Designation for Toca 511 in HGG, but this is no assurance we will receive these designations for any future product candidates. Further, even though we have received these designations for Toca 511 & Toca FC, we may not experience a faster development process, review or approval compared to conventional FDA or EMA procedures. The FDA or EMA may withdraw these designations if it believes that they are no longer supported by data from our clinical development program.

We and our contract manufacturers are subject to significant regulation with respect to manufacturing our products. The manufacturing facilities on which we rely may not continue to meet regulatory requirements and have limited capacity.

We currently have relationships with a limited number of suppliers for the manufacturing of our viral vectors and product candidates. Each supplier may require licenses to manufacture such components if such processes are not owned by the supplier or in the public domain and we may be unable to transfer or sublicense the intellectual property rights we may have or later obtain with respect to such activities.

All entities involved in the preparation of therapeutics for clinical trials or commercial sale, including our existing contract manufacturers for our product candidates, are subject to extensive regulation. Components of a finished therapeutic product approved for commercial sale or used in late-stage clinical trials must be manufactured in accordance with cGMP. These regulations govern manufacturing processes and procedures (including record keeping) and the implementation and operation of quality systems to control and assure the quality of investigational products and products approved for sale. Poor control of production processes can lead to the introduction of adventitious agents or other contaminants, or to inadvertent changes in the properties or stability of our product candidates that may not be detectable in final product testing. We or our contract manufacturers must supply all necessary documentation in support of a BLA on a timely basis and must adhere to the FDA's good laboratory practices and cGMP regulations enforced by the FDA through its facilities inspection program. Some of our contract manufacturers have limited experience in production of commercially-approved products and therefore may have not obtained the requisite FDA approvals to do so. Our facilities and quality systems and the facilities and quality systems of some or all of our third-party contractors must pass a pre-approval inspection for compliance with the applicable regulations as a condition of regulatory approval of our product candidates or any of our other potential products. In addition, the regulatory authorities may, at any time, audit or inspect a manufacturing facility involved with the preparation of our product candidates or our other potential products or the associated quality systems for compliance with the regulations applicable to the activities being conducted. If these facilities do not pass a pre-approval plant inspection, FDA approval of the products may not be granted.

The regulatory authorities also may, at any time following approval of a product for sale, audit our manufacturing facilities or those of our third-party contractors. If any such inspection or audit identifies a failure to comply with applicable regulations or if a violation of our product specifications or applicable regulations occurs independent of such an inspection or audit, we or the relevant regulatory authority may require remedial measures that may be costly and/or time-consuming for us or a third party to implement and that may include the temporary or permanent suspension of a clinical trial or commercial sales or the temporary or permanent closure of a facility. Any such remedial measures imposed upon us or third parties with whom we contract could materially harm our business.

If we or any of our third-party manufacturers fail to maintain regulatory compliance, the FDA can impose regulatory sanctions including, among other things, refusal to approve a pending application for a new drug product or biologic product or revocation of a pre-existing approval. As a result, our business, financial condition and results of operations may be materially harmed.

Additionally, if supply from one approved manufacturer is interrupted, there could be a significant disruption in commercial supply. An alternative manufacturer would need to be qualified through a BLA supplement which could result in further delay. The regulatory agencies may also require additional studies if a new manufacturer is relied upon for commercial production. Switching manufacturers may involve substantial costs and is likely to result in a delay in our desired clinical and commercial timelines.

These factors could cause the delay of clinical trials, regulatory submissions, required approvals or commercialization of our product candidates, cause us to incur higher costs and prevent us from commercializing our products successfully. Furthermore, if our suppliers fail to meet contractual requirements, and we are unable to secure one or more replacement suppliers capable of production at a substantially equivalent cost, our clinical trials may be delayed or we could lose potential revenue.

Our Toca 511 & Toca FC product may face competition sooner than anticipated, if approved.

The Biologics Price Competition and Innovation Act, or BPCIA, created an abbreviated approval pathway for biological products that are biosimilar to or interchangeable with an FDA-licensed reference biological product. Under the BPCIA, an application for a biosimilar product may not be submitted to the FDA until four years following the date that the reference product was first licensed by the FDA. In addition, the approval of a biosimilar product may not be made effective by the FDA until 12 years from the date on which the reference product was first licensed. During this 12-year period of exclusivity, another company may still market a competing version of the reference product if the FDA approves a full BLA for the competing product containing the sponsor's own preclinical data and data from adequate and well-controlled clinical trials to demonstrate the safety, purity and potency of its product.

We believe that any of our product candidates approved as a biological product under a BLA should qualify for the 12-year period of exclusivity. However, there is a risk that this exclusivity could be shortened due to congressional action or otherwise, or that the FDA will not consider our product candidates to be reference products for competing products, potentially creating the opportunity for competition sooner than anticipated. Other aspects of the BPCIA, some of which may impact the BPCIA exclusivity provisions, have also been the subject of recent litigation. Moreover, the extent to which a biosimilar, once approved, will be substituted for any one of our reference products in a way that is similar to traditional generic substitution for non-biological products is not yet clear, and will depend on a number of marketplace and regulatory factors that are still developing.

We may be subject, directly or indirectly, to federal, state, local and foreign healthcare fraud and abuse laws, false claims laws, privacy laws and other applicable healthcare laws, and the failure to comply with such laws could result in substantial penalties. Our employees, independent contractors, consultants, principal investigators, CROs, commercial partners and vendors may engage in misconduct or other improper activities, including noncompliance with regulatory standards and requirements.

We are exposed to the risk of fraud, misconduct or other illegal activity by our employees, independent contractors, consultants, principal investigators, CROs, commercial partners and vendors. Misconduct by these parties could include intentional, reckless and/or negligent conduct that fails to: comply with the laws of the FDA and other similar foreign regulatory bodies; provide true, complete and accurate information to the FDA and other similar foreign regulatory bodies; comply with manufacturing standards we have established; comply with federal and state data privacy, security, fraud and abuse and other healthcare laws and regulations in the United States and similar foreign fraudulent misconduct laws; or report financial information or data accurately or to disclose unauthorized activities to us.

In addition, our current and future operations are subject to regulation under such laws, and if we obtain FDA approval for any of our product candidates and begin commercializing those products in the United States, our potential exposure under such laws would increase significantly, along with our costs associated with compliance with such laws. These laws may impact, among other things, our current activities with principal investigators and research patients, as well as proposed and future sales, marketing and education programs. In particular, the promotion, sales and marketing of healthcare items and services, as well as certain business arrangements in the healthcare industry, are subject to extensive laws and regulations intended to prevent fraud, misconduct, kickbacks, self-dealing and other abusive practices. These laws and regulations may restrict or prohibit a wide range of pricing, discounting, marketing and promotion, including off-label promotion of our products, structuring of commission(s), certain customer incentive programs and other business arrangements generally. Activities subject to these laws also involve the improper use or misrepresentation of information obtained in the course of patient recruitment for clinical trials, creating fraudulent data in our preclinical studies or clinical trials or illegal misappropriation of drug product, which could result in regulatory sanctions and cause serious harm to our reputation. The laws that may affect our ability to operate include, but are not limited to:

- the federal Anti-Kickback Statute, which prohibits, among other things, individuals and entities from knowingly and willfully soliciting, receiving, offering or paying any remuneration (including any kickback, bribe, or rebate), directly or indirectly, overtly or covertly, in cash or in kind, to induce, or in return for, either the referral of an individual for, or the purchase, lease, order or recommendation of, any good, facility, item or service for which payment may be made, in whole or in part, under a federal healthcare program, such as the Medicare and Medicaid programs. A person or entity does not need to have actual knowledge of the statute or specific intent to violate it in order to have committed a violation;
- federal civil and criminal false claims laws and civil monetary penalty laws, including the federal civil False Claims Act, which impose criminal and civil penalties, through government, civil whistleblower or *qui tam* actions, on individuals and entities for, among other things, knowingly presenting, or causing to be presented, claims for payment or approval from Medicare, Medicaid, or other federal healthcare programs that are false, fictitious or fraudulent, or knowingly making, using or causing to be made or used, a false statement to avoid, decrease or conceal an obligation to pay money to the federal government. In addition, the government may assert that a claim including items and services resulting from a violation of the federal Anti-Kickback Statute constitutes a false or fraudulent claim for purposes of the federal civil False Claims Act;
- the federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, which imposes criminal and civil liability for, among other things, knowingly and willfully executing, or attempting to execute, a scheme to defraud any healthcare benefit program or obtain, by means of false or fraudulent pretenses, representations, or promises, any of the money or property owned by, or under the custody or control of, any healthcare benefit program, regardless of the payor (e.g., public or private), willfully obstructing a criminal investigation of a healthcare offense, and knowingly and willfully falsifying, concealing or covering up by any trick or device a material fact or making any materially false, fictitious or fraudulent statements in connection with the delivery of, or payment for, healthcare benefits, items or services relating to healthcare matters. Similar to the federal Anti-Kickback Statute, a person or entity does not need to have actual knowledge of the statute or specific intent to violate it in order to have committed a violation;

- HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act, or HITECH, and their respective implementing regulations, which impose requirements on certain covered healthcare providers, health plans, and healthcare clearinghouses, as well as their respective business associates that perform services for them that involve the creation, use, maintenance or disclosure of, individually identifiable health information, relating to the privacy, security and transmission of individually identifiable health information without appropriate authorization;
- the federal physician payment transparency requirements, sometimes referred to as the "Physician Payments Sunshine Act," created under the Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act, collectively the Affordable Care Act, and its implementing regulations, which require certain manufacturers of drugs, devices, biologics and medical supplies for which payment is available under Medicare, Medicaid or the Children's Health Insurance Program (with certain exceptions) to report annually to the Centers for Medicare and Medicaid Services, or CMS, information related to payments or other transfers of value made to physicians (defined to include doctors, dentists, optometrists, podiatrists and chiropractors) and teaching hospitals, as well as ownership and investment interests held by physicians and their immediate family members;
- the U.S. Federal Food, Drug and Cosmetic Act, or FD&C Act, which prohibits, among other things, the adulteration or misbranding of drugs and medical devices; and
- federal consumer protection and unfair competition laws, which broadly regulate marketplace activities and activities that potentially harm consumers.

Additionally, we are subject to state, local and foreign equivalents of each of the healthcare fraud and abuse laws described above, among others, some of which may be broader in scope and may apply regardless of the payor. We may also be subject to state, local and foreign laws that require pharmaceutical companies to comply with the pharmaceutical industry's voluntary compliance guidelines and the relevant compliance guidance promulgated by the federal government or otherwise restrict payments that may be made to healthcare providers; to report information related to payments and other transfers of value to healthcare providers or entities, or marketing expenditures; report certain information regarding drug pricing; and require registration of pharmaceutical sales representatives. We may also be subject to state and foreign laws governing the privacy and security of health information in certain circumstances, many of which differ from each other in significant ways and often are not preempted by HIPAA, thus complicating compliance efforts.

In the European Union, the General Data Protection Regulation (2016/679), or GDPR, applies to any organization established in the European Union, as well as to those outside of the European Union if they collect and use "personal data", or any information relating to an identified or identifiable natural person, in connection with the offering of goods or services to individuals in the European Union or the monitoring of their behavior Under the GDPR, fines of up to 20 million Euros or up to 4% of the annual global turnover of the infringer, whichever is greater, could be imposed for significant non-compliance. Additionally, California recently enacted legislation that has been dubbed the first "GDPR-like" law in the United States. Known as the California Consumer Privacy Act, or CCPA, it creates new individual privacy rights for consumers (as that word is broadly defined in the law) and places increased privacy and security obligations on entities handling personal data of consumers or households. When it goes into effect on January 1, 2020, the CCPA will require covered companies to provide new disclosures to California consumers, provide such consumers new ways to opt-out of certain sales of personal information, and allow for a new cause of action for data breaches. Legislators have stated that amendments will be proposed to the CCPA before it goes into effect, but it remains unclear what, if any, modifications will be made to this legislation or how it will be interpreted. As currently written, the CCPA will likely impact our business activities and exemplifies the vulnerability of our business to not only cyber threats but also the evolving regulatory environment related to personal data and protected health information.

It is not always possible to identify and deter employee misconduct, and the precautions we take to detect and prevent inappropriate conduct may not be effective in controlling unknown or unmanaged risks or losses or in protecting us from governmental investigations or other actions or lawsuits stemming from a failure to be in compliance with such laws or regulations. We are also subject to the risk that a person or government could allege such fraud or other misconduct, even if none occurred. Efforts to ensure that our business arrangements will comply with applicable healthcare laws and regulations will involve substantial costs. It is possible that governmental and enforcement authorities will conclude that our business practices may not comply with current or future statutes, regulations or case law interpreting applicable fraud and abuse or other healthcare laws and regulations. If any such actions are instituted against us, and we are not successful in defending ourselves or asserting our rights, those actions could have a significant impact on our business, including the imposition of civil, criminal and administrative penalties, damages, disgorgement, monetary fines, possible exclusion from participation in Medicare, Medicaid and other federal healthcare programs, contractual damages, reputational harm, diminished profits and future earnings, individual imprisonment, additional reporting obligations and oversight if we become subject to a corporate integrity agreement or other agreement to resolve allegations of non-compliance with these laws, and curtailment or restructuring of our operations, any of which could adversely affect our ability to operate our business and our results of operations. In addition, the approval and commercialization of any of our product candidates outside the United States will also likely subject us to foreign equivalents of the healthcare laws mentioned above, among other foreign laws.

Coverage and reimbursement may be limited or unavailable in certain market segments for our product candidates, if approved, which could make it difficult for us to sell our product candidates profitably.

Successful sales of our product candidates, if approved, depend on the availability of coverage and adequate reimbursement from third-party payors such as government authorities, including Medicare and Medicaid, private health insurers, and health maintenance organizations. Because our product candidates represent new approaches to the treatment of cancer, we cannot be sure that coverage and reimbursement will be available for, or accurately estimate the potential revenue from, our product candidates.

Patients who are provided medical treatment for their conditions generally rely on third-party payors to reimburse all or part of the costs associated with their treatment. Coverage and adequate reimbursement from governmental healthcare programs, such as Medicare and Medicaid, and commercial payors are critical to new product acceptance.

Third-party payors decide which drugs and treatments they will cover and the amount of reimbursement. Coverage and reimbursement by a third-party payor may depend upon a number of factors, including, but not limited to, the third-party payor's determination that use of a product is:

- a covered benefit under its health plan;
- safe, effective and medically necessary;
- appropriate for the specific patient;
- cost-effective; and
- neither experimental nor investigational.

In the United States, no uniform policy of coverage and reimbursement for products exists among third-party payors, and coverage and reimbursement for products can differ significantly from payor to payor. As a result, obtaining coverage and reimbursement approval of a product from a government or other third-party payor is a time-consuming and costly process that could require us to provide to each payor supporting scientific, clinical and cost-effectiveness data for the use of our products and to justify the level of coverage and reimbursement relative to other therapies, with no assurance that coverage and adequate reimbursement will be obtained. Third party payors may also have difficulty in determining the appropriate coverage of our product candidates, if approved, due to the fact that they are combination products that include a small molecule drug. To the extent there are any delays in determining such coverage or inadequate coverage and reimbursement for all aspects of our combination therapies, it would adversely affect the market acceptance, demand and use of our product candidates.

A number of gene therapy products have been approved recently by the FDA. Although CMS subsequently approved a method of coverage and reimbursement for certain gene therapy products, it is difficult to predict how CMS may decide to cover and reimburse our product candidates, if approved. Often private payors follow the coverage and reimbursement decisions of the Medicare program, but also have their own methods and approval process. Therefore, coverage and reimbursement for can differ significantly from payor to payor and approval by one payor does not guarantee approval by another. Further, third-party payors' coverage and reimbursement determinations are subject to change. Any denial in coverage or reduction in reimbursement from Medicare or other government programs may result in a similar denial or reduction in payments from private payors, which may adversely affect our future profitability.

We intend to seek approval to market our product candidates in both the United States and in selected foreign jurisdictions. If we obtain approval in one or more foreign jurisdictions for our product candidates, we will be subject to rules and regulations in those jurisdictions. In some foreign countries, particularly those in the European Union, the pricing of biologics is subject to governmental control and other market regulations which could put pressure on the pricing and usage of our product candidates. In these countries, pricing negotiations with governmental authorities can take considerable time after obtaining marketing approval of a product candidate. In addition, market acceptance and sales of our product candidates will depend significantly on the availability of coverage and adequate reimbursement from third-party payors for our product candidates and may be affected by existing and future health care reform measures.

Healthcare legislative reform measures may have a material adverse effect on our business and results of operations.

Third-party payors, whether domestic or foreign, or governmental or commercial, are developing increasingly sophisticated methods of controlling healthcare costs. In both the United States and certain foreign jurisdictions, there have been a number of legislative and regulatory changes to the health care system that could impact our ability to sell our products profitably. In particular, in 2010, the Affordable Care Act was enacted in the United States. The Affordable Care Act and its implementing regulations, among other things, subjected biological products to potential competition by lower-cost biosimilars, revised the methodology by which rebates owed by manufacturers under the Medicaid Drug Rebate Program are calculated for certain drugs and biologics, including our product candidates, that are inhaled, infused, instilled, implanted or injected, increased the minimum Medicaid rebates owed by most manufacturers under the Medicaid Drug Rebate Program, extended the Medicaid Drug Rebate program to utilization of prescriptions of individuals enrolled in Medicaid managed care organizations, subjected manufacturers to new annual fees and taxes for certain branded prescription drugs, and provided incentives to programs that increase the federal government's comparative effectiveness research.

Since its enactment, there have been judicial, Congressional and political challenges to certain aspects of the Affordable Care Act, as well as recent efforts by the Trump administration to repeal or replace certain aspects of the Affordable Care Act. Since January 2017, President Trump has signed two Executive Orders and other directives designed to delay the implementation of certain provisions of the Affordable Care Act or otherwise circumvent some of the requirements for health insurance mandated by the Affordable Care Act. Concurrently, Congress has considered legislation that would repeal or repeal and replace all or part of the Affordable Care Act. While Congress has not passed comprehensive repeal legislation, two bills affecting the implementation of certain taxes under the Affordable Care Act have been signed into law. On December 22, 2017, President Trump signed into law new federal tax legislation, informally titled the Tax Cuts and Jobs Act, or Tax Act, which includes a provision repealing, effective January 1, 2019, the tax-based shared responsibility payment imposed by the Affordable Care Act on certain individuals who fail to maintain qualifying health coverage for all or part of a year that is commonly referred to as the "individual mandate". On January 22, 2018, President Trump signed a continuing resolution on appropriations for fiscal year 2018 that delayed the implementation of certain Affordable Care Act-mandated fees, including the so-called "Cadillac" tax on certain high cost employer-sponsored insurance plans, the annual fee imposed on certain health insurance providers based on market share, and the medical device excise tax on non-exempt medical devices. The Bipartisan Budget Act of 2018, or the BBA, among other things, amended the Affordable Care Act, effective January 1, 2019, to close the coverage gap in most Medicare Part D drug plans, commonly referred to as the "donut hole". In July 2018, CMS published a final rule permitting further collections and payments to and from certain Affordable Care Act qualified health plans and health insurance issuers under the Affordable Care Act risk adjustment program in response to the outcome of federal district court litigation regarding the method CMS uses to determine this risk adjustment. On December 14, 2018, a Texas U.S. District Court Judge ruled that the Affordable Care Act is unconstitutional in its entirety because the "individual mandate" was repealed by Congress as part of the Tax Act. While the Texas U.S. District Court Judge, as well as the Trump administration and CMS, have stated that the ruling will have no immediate effect pending appeal of the decision, it is unclear how this decision, subsequent appeals, and other efforts to repeal and replace the Affordable Care Act will impact the Affordable Care Act and our business.

In addition, other legislative changes have been proposed and adopted in the United States since the Affordable Care Act was enacted. In August 2011, the Budget Control Act of 2011, among other things, created measures for spending reductions by Congress. A Joint Select Committee on Deficit Reduction, tasked with recommending a targeted deficit reduction of at least $1.2 trillion for the years 2013 through 2021, was unable to reach required goals, thereby triggering the legislation's automatic reduction to several government programs. This includes aggregate reductions of Medicare payments to providers up to 2% per fiscal year, which went into effect on April 1, 2013 and, due to subsequent legislation, including the BBA, will stay in effect through 2027 unless Congressional action is taken. In January 2013, President Obama signed into law the American Taxpayer Relief Act of 2012, which, among other things, reduced Medicare payments to several providers, including hospitals, imaging centers and cancer treatment centers, and increased the statute of limitations period for the government to recover overpayments to providers from three to five years. Moreover, payment methodologies including payment for any companion diagnostics may be subject to changes in healthcare legislation and regulatory initiatives. For example, CMS began bundling the Medicare payments for certain laboratory tests ordered while a patient received services in a hospital outpatient setting and, beginning in 2018, CMS has begun paying for clinical laboratory services based on a weighted-average of reported prices that private payors, Medicare Advantage plans and Medicaid Managed Care plans pay for laboratory services.

Further recently, there has been heightened governmental scrutiny over the manner in which drug manufacturers set prices for their marketed products, which has resulted in several Congressional inquiries and proposed and enacted federal and state legislation designed to, among other things, bring more transparency to product pricing, review the relationship between pricing and manufacturer patient programs, and reform government program reimbursement methodologies for drug products. At the federal level, the Trump administration's budget proposal for fiscal year 2019 contains further product price control measures that could be enacted during the 2019 budget process or in other future legislation, including, for example, measures to permit Medicare Part D plans to negotiate the price of certain products under Medicare Part B, to allow some states to negotiate product prices under Medicaid, and to eliminate cost sharing for generic products for low-income patients. Further, the Trump administration released a "Blueprint", or plan, to lower drug prices and reduce out of pocket costs of drugs that contains additional proposals to increase drug manufacturer

competition, increase the negotiating power of certain federal healthcare programs, incentivize manufacturers to lower the list price of their products, and reduce the out of pocket costs of drug products paid by consumers. The United States Department of Health and Human Services, or HHS, has already started the process of soliciting feedback on some of these measures and are implementing others under its existing authority. For example, in September 2018, CMS announced that it will allow Medicare Advantage Plans the option to use step therapy for Part B drugs beginning January 1, 2019, and in October 2018, CMS proposed a new rule that would require direct-to-consumer television advertisements of prescription drugs and biological products, for which payment is available through or under Medicare or Medicaid, to include in the advertisement the Wholesale Acquisition Cost, or list price, of that drug or biological product. On January 31, 2019, the HHS Office of Inspector General proposed modifications to federal Anti-Kickback Statute safe harbors which, among other things, may affect rebates paid by manufacturers to Medicare Part D plans, the purpose of which is to further reduce the cost of drug products to consumers. While some of these and other proposed measures will require authorization through additional legislation to become effective, Congress and the Trump administration have each indicated that it will continue to seek new legislative and/or administrative measures to control drug costs. At the state level, legislatures are increasingly passing legislation and implementing regulations designed to control pharmaceutical and biological product pricing, including price or patient reimbursement constraints, discounts, restrictions on certain product access and marketing cost disclosure and transparency measures, and, in some cases, designed to encourage importation from other countries and bulk purchasing.

Further, on May 30, 2018, the Trickett Wendler, Frank Mongiello, Jordan McLinn, and Matthew Bellina Right to Try Act of 2017, or Right to Try Act, was signed into law. The law, among other things, provides a federal framework for certain patients to access certain investigational new drug products that have completed a Phase I clinical trial and that are undergoing investigation for FDA approval. Under certain circumstances, eligible patients can seek treatment without enrolling in clinical trials and without obtaining FDA permission under the FDA expanded access program. There is no obligation for a drug manufacturer to make its drug products available to eligible patients as a result of the Right to Try Act.

There have been, and likely will continue to be, legislative and regulatory proposals at the foreign, federal and state levels directed at broadening the availability of healthcare and containing or lowering the cost of healthcare. We cannot predict the initiatives that may be adopted in the future. The continuing efforts of the government, insurance companies, managed care organizations and other payors of healthcare services to contain or reduce costs of healthcare and/or impose price controls may adversely affect:

- the demand for our product candidates, if we obtain regulatory approval;
- our ability to set a price that we believe is fair for our products;
- our ability to generate revenue and achieve or maintain profitability;
- the level of taxes that we are required to pay; and
- the availability of capital.

Due to the novel nature of our technology and the small size of our initial target patient populations, we face uncertainty related to pricing and reimbursement for these product candidates.

Our initial target patient populations are relatively small. As a result, the pricing and reimbursement of our product candidates, if approved, must be adequate to support commercial infrastructure. If we are unable to obtain adequate levels of reimbursement, our ability to successfully market and sell our product candidates will be adversely affected. The manner and level at which reimbursement is provided for services related to our product candidates (e.g., for administration of our product to patients) is also important. Inadequate reimbursement for such services may lead to physician resistance and adversely affect our ability to market or sell our products.

If we fail to comply with environmental, health and safety laws and regulations, we could become subject to fines or penalties or incur costs that could have a material adverse effect on the success of our business.

Our research and development, manufacturing processes, clinical trials and products may involve the controlled use of hazardous materials, chemicals, viruses and various radioactive compounds. Specifically, if our products or product candidates spread from human or companion pet patients to other people or pets, these other individuals or pets (such as the immune suppressed or the very young), might be more sensitive to the product or product candidate than the patient and may experience an adverse reaction. We are subject to federal, state and local laws and regulations governing the use, manufacture, storage, handling and disposal of such materials and certain waste products, including numerous environmental, health and safety laws and regulations, such as those governing laboratory procedures and the handling, use, storage, treatment and disposal of hazardous materials and wastes. Our operations involve the use of hazardous and flammable materials, including chemicals and biological materials. Our operations also produce hazardous waste products. We generally contract with third parties for the disposal of these materials and wastes. We cannot eliminate the risk of contamination or injury from these materials. In the event of contamination or injury resulting from our use of hazardous materials, we could be held liable for any resulting damages, and any liability could exceed our resources. We also could incur significant costs associated with civil or criminal fines and penalties.

Although we maintain workers' compensation insurance to cover us for costs and expenses we may incur due to injuries to our employees resulting from the use of hazardous materials or other work-related injuries, this insurance may not provide adequate coverage against potential liabilities. In addition, we may incur substantial costs in order to comply with current or future environmental, health and safety laws and regulations. These current or future laws and regulations may impair our research, development or production efforts. Failure to comply with these laws and regulations also may result in substantial fines, penalties or other sanctions.

Risks related to our intellectual property

If we are unable to protect our intellectual property rights or if our intellectual property rights are inadequate for our technology and product candidates, our competitive position could be harmed.

Our commercial success will depend in part on our ability to obtain and maintain patent and other intellectual property protection in the United States and other countries with respect to our proprietary technology and products. We rely on trade secret, patent, copyright and trademark laws, and confidentiality, licensing and other agreements with employees and third parties, all of which offer only limited protection. We seek to protect our proprietary position by filing and prosecuting patent applications in the United States and abroad related to our novel technologies and products that are important to our business.

The patent positions of biotechnology and pharmaceutical companies generally are highly uncertain, involve complex legal and factual questions and have in recent years been the subject of much litigation. As a result, the issuance, scope, validity, enforceability and commercial value of our patents, including those patent rights licensed to us by third parties, are highly uncertain. The steps we or our licensors have taken to protect our proprietary rights may not be adequate to preclude misappropriation of our proprietary information or infringement of our intellectual property rights, both inside and outside of the United States. Further, the examination process may require us or our licensors to narrow the claims for our pending patent applications, which may limit the scope of patent protection that may be obtained if these applications issue. The rights already granted under any of our currently issued patents or those licensed to us and those that may be granted under future issued patents may not provide us with the proprietary protection or competitive advantages we are seeking. If we or our licensors are unable to obtain and maintain patent protection for our technology and products, or if the scope of the patent protection obtained is not sufficient, our competitors could develop and commercialize technology and products similar or superior to ours, and our ability to successfully commercialize our technology and products may be adversely affected. It is also possible that we or our licensors will fail to identify patentable aspects of inventions made in the course of our development and commercialization activities before it is too late to obtain patent protection on them. It is also possible that as research and development progresses, the direction of our intellectual property strategy and patent portfolio will change, resulting in strategic business decisions to allow certain patents or patent applications to be abandoned or lapse.

With respect to patent rights, we do not know whether any of the pending patent applications for any of our compounds or biologic products will result in the issuance of patents that effectively protect our technology or products, or if any of our issued patents or if any of our or our licensors' issued patents will effectively prevent others from commercializing competitive technologies and products. Publications of discoveries in the scientific literature often lag behind the actual discoveries, and patent applications in the United States and other jurisdictions are typically not published until 18 months after filing or in some cases not at all, until they are issued as a patent. Therefore, we cannot be certain that we or our licensors were the first to make the inventions claimed in our owned or licensed patents or pending patent applications, or that we or our licensors were the first to file for patent protection of such inventions.

Our pending applications cannot be enforced against third parties practicing the technology claimed in such applications unless and until a patent issues from such applications. Because the issuance of a patent is not conclusive as to its inventorship, scope, validity or enforceability, issued patents that we own or have licensed from third parties may be challenged in the courts or patent offices in the United States and abroad. Such challenges may result in the loss of patent protection, the narrowing of claims in such patents or the invalidity or unenforceability of such patents, which could limit our ability to stop others from using or commercializing similar or identical technology and products, or limit the duration of the patent protection for our technology and products. Protecting against the unauthorized use of our or our licensor's patented technology, trademarks and other intellectual property rights is expensive, difficult and may in some cases not be possible. In some cases, it may be difficult or impossible to detect third-party infringement or misappropriation of our intellectual property rights, even in relation to issued patent claims, and proving any such infringement may be even more difficult.

Third-party claims of intellectual property infringement may prevent or delay our development and commercialization efforts.

Our commercial success depends in part on our avoiding infringement of the patents and proprietary rights of third parties. There is a substantial amount of litigation, both within and outside the United States, involving patent and other intellectual property rights in the biotechnology and pharmaceutical industries, including patent infringement lawsuits, interferences, oppositions and inter partes reexamination proceedings before the U.S. Patent and Trademark Office, or U.S. PTO, and corresponding foreign patent offices. Numerous U.S. and foreign issued patents and pending patent applications, which are owned by third parties, exist in the fields in which we are pursuing development candidates. As the biotechnology and pharmaceutical industries expand and more patents are issued, the risk increases that our product candidates may be subject to claims of infringement of the patent rights of third parties.

Third parties have asserted, and in the future may assert, that we are employing their proprietary technology without authorization. There may be third-party patents or patent applications with claims to materials, formulations, methods of manufacture or methods for treatment related to the use or manufacture of our product candidates. Because patent applications can take many years to issue, there may be currently pending patent applications which may later result in issued patents that our product candidates may infringe. In addition, third parties may obtain patents in the future and claim that use of our technologies infringes upon these patents. If any third-party patents were held by a court of competent jurisdiction to cover the manufacturing process of any of our product candidates, or any final product itself, the holders of any such patents may be able to block our ability to commercialize such product candidate unless we obtained a license under the applicable patents, or until such patents expire.

Similarly, if any third-party patents were held by a court of competent jurisdiction to cover aspects of our formulations, processes for manufacture or methods of use, including combination therapy, the holders of any such patents may be able to block our ability to develop and commercialize the applicable product candidate unless we obtained a license or until such patent expires. In either case, such a license may not be available on commercially reasonable terms or at all.

Parties making claims against us may obtain injunctive or other equitable relief, which could effectively block our ability to further develop and commercialize one or more of our product candidates. Defense of these claims, regardless of their merit, may involve substantial litigation expense and would be a substantial diversion of employee resources from our business. In the event of a successful claim of infringement against us, we may have to pay substantial damages, including treble damages and attorneys' fees for willful infringement, pay royalties, redesign our infringing products or obtain one or more licenses from third parties, which may be impossible or require substantial time and monetary expenditure.

We may not be successful in obtaining or maintaining necessary rights to gene therapy product components and processes for our development pipeline through acquisitions and in-licenses.

Presently we believe that we have rights to the intellectual property, through licenses from third parties and under patents that we own, to develop our gene therapy product candidates. Because our programs may involve additional product candidates that may require the use of proprietary rights held by third parties, the growth of our business may depend in part on our ability to acquire, in-license or use these proprietary rights. In addition, our product candidates may require specific formulations to work effectively and efficiently and these rights may be held by others. We may be unable to acquire or in-license any compositions, methods of use, processes or other third-party intellectual property rights from third parties that we identify. The licensing and acquisition of third-party intellectual property rights is a competitive area, and a number of more established companies are also pursuing strategies to license or acquire third-party intellectual property rights that we may consider attractive. These established companies may have a competitive advantage over us due to their size, cash resources and greater clinical development and commercialization capabilities.

In addition, companies that perceive us to be a competitor may be unwilling to assign or license rights to us. We also may be unable to license or acquire third-party intellectual property rights on terms that would allow us to make an appropriate return on our investment. If we are unable to successfully obtain rights to required third-party intellectual property rights, our business, financial condition and prospects for growth could suffer.

If we fail to comply with our obligations in the agreement under which we license intellectual property rights from the University of Southern California, or USC, or otherwise experience disruptions to our business relationships with USC or other future licensors, we could lose license rights that are important to our business.

In October 2007, we entered into a license agreement with USC pursuant to which we received a worldwide, exclusive license to, among other things, manufacture and market products utilizing certain inventions that are critical to our business. We expect to enter into additional license agreements in the future. Our existing license agreement imposes, and we expect that future license agreements will impose, various diligence, milestone payment, royalty and other obligations on us. If we fail to comply with our obligations under these agreements, or we are subject to a bankruptcy, the licensor may have the right to terminate the license, in which event we would not be able to market products covered by the license.

We may need to obtain licenses from third parties to advance our research or allow commercialization of our product candidates, and we have done so from time to time. We may fail to obtain any of these licenses at a reasonable cost or on reasonable terms, if at all. In that event, we may be required to expend significant time and resources to develop or license replacement technology. If we are unable to do so, we may be unable to develop or commercialize the affected product candidates, which could harm our business significantly. We cannot provide any assurances that third-party patents do not exist which might be enforced against our current product candidates or future products, resulting in either an injunction prohibiting our sales, or, with respect to our sales, an obligation on our part to pay royalties and/or other forms of compensation to third parties.

In certain cases, patent prosecution of our licensed technology may be controlled solely by the licensor. If our licensors fail to obtain and maintain patent or other protection for the proprietary intellectual property we license from them, we could lose our rights to the intellectual property or our exclusivity with respect to those rights, and our competitors could market competing products using the intellectual property. In certain cases, we control the prosecution of patents resulting from licensed technology. In the event we breach any of our obligations related to such prosecution, we may incur significant liability to our licensing partners. Licensing of intellectual property is of critical importance to our business and involves complex legal, business and scientific issues and is complicated by the rapid pace of scientific discovery in our industry. Disputes may arise regarding intellectual property subject to a licensing agreement, including:

- the scope of rights granted under the license agreement and other interpretation-related issues;
- the extent to which our technology and processes infringe on intellectual property of the licensor that is not subject to the licensing agreement;
- the sublicensing of patent and other rights under our collaborative development relationships;
- our diligence obligations under the license agreement and what activities satisfy those diligence obligations;
- the ownership of inventions and know-how resulting from the joint creation or use of intellectual property by our licensors and us and our partners; and
- the priority of invention of patented technology.

If disputes over intellectual property that we have licensed prevent or impair our ability to maintain our current licensing arrangements on acceptable terms, we may be unable to successfully develop and commercialize the affected product candidates.

We may be involved in lawsuits to protect or enforce our patents or the patents of our licensors, which could be expensive, time-consuming and unsuccessful.

Competitors may infringe our patents or the patents of our licensors. To counter infringement or unauthorized use, we may be required to file infringement claims, which can be expensive and time-consuming. In addition, in an infringement proceeding, a court may decide that a patent of ours or our licensors is not valid, is unenforceable and/or is not infringed, or may refuse to stop the other party from using the technology at issue on the grounds that our patents do not cover the technology in question. An adverse result in any litigation or defense proceedings could put one or more of our patents at risk of being invalidated or interpreted narrowly and could put our patent applications at risk of not issuing.

Interference or derivation proceedings provoked by third parties or brought by us may be necessary to determine the priority of inventions with respect to our patents or patent applications or those of our licensors. An unfavorable outcome could require us to cease using the related technology or to attempt to license rights to it from the prevailing party. Our business could be harmed if the prevailing party does not offer us a license on commercially reasonable terms. Our defense of litigation, interference or derivation proceedings may fail and, even if successful, may result in substantial costs and distract our management and other employees. We may not be able to prevent, alone or with our licensors, misappropriation of our intellectual property rights, particularly in countries where the laws may not protect those rights as fully as in the United States.

Furthermore, because of the substantial amount of discovery required in connection with intellectual property litigation, there is a risk that some of our confidential information could be compromised by disclosure during this type of litigation. There could also be public announcements of the results of hearings, motions or other interim proceedings or developments. If securities analysts or investors perceive these results to be negative, it could have a material adverse effect on the price of our common stock.

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

Periodic maintenance fees, renewal fees, annuity fees and various other governmental fees on patents and/or applications will be due to be paid to the U.S. PTO and various governmental patent agencies outside of the United States in several stages over the lifetime of the patents and/or applications. We employ an outside firm and rely on our outside counsel to pay these fees due to non-U.S. patent agencies. The U.S. PTO and various non-U.S. governmental patent agencies require compliance with a number of procedural, documentary, fee payment and other similar provisions during the patent application process. We employ reputable law firms and other professionals to help us comply, and in many cases, an inadvertent lapse can be cured by payment of a late fee or by other means in accordance with the applicable rules. However, there are situations in which non-compliance can result in abandonment or lapse of the patent or patent application, resulting in partial or complete loss of patent rights in the relevant jurisdiction. In such an event, our competitors might be able to enter the market and this circumstance would have a material adverse effect on our business.

Issued patents covering our product candidates could be found invalid or unenforceable if challenged in court.

If we, USC or one of our future licensing partners initiated legal proceedings against a third party to enforce a patent covering one of our product candidates, the defendant could counterclaim that the patent covering our product candidate is invalid and/or unenforceable. In patent litigation in the United States, defendant counterclaims alleging invalidity and/or unenforceability are commonplace. Grounds for a validity challenge could be an alleged failure to meet any of several statutory requirements, including lack of novelty, obviousness or non-enablement. Grounds for an unenforceability assertion could be an allegation that someone connected with prosecution of the patent withheld relevant information from the U.S. PTO, or made a misleading statement, during prosecution. Third parties may also raise similar claims before administrative bodies in the United States or abroad, even outside the context of litigation. Such mechanisms include re-examination, post grant review and equivalent proceedings in foreign jurisdictions (e.g., opposition proceedings). Such proceedings could result in revocation or amendment to our patents in such a way that they no longer cover our product candidates. The outcome following legal assertions of invalidity and unenforceability is unpredictable. With respect to the validity question, for example, we cannot be certain that there is no invalidating prior art, of which we and the patent examiner were unaware during prosecution. If a defendant were to prevail on a legal assertion of invalidity and/or unenforceability, we would lose at least part, and perhaps all, of the patent protection on our product candidates. Such a loss of patent protection would have a material adverse impact on our business.

We may be subject to claims that our employees, consultants or independent contractors have wrongfully used or disclosed confidential information of third parties or that our employees have wrongfully used or disclosed alleged trade secrets of their former employers.

We employ individuals who were previously employed at universities or other biotechnology or pharmaceutical companies, including our competitors or potential competitors. Although we try to ensure that our employees, consultants and independent contractors do not use the proprietary information or know-how of others in their work for us, we may be subject to claims that we or our employees, consultants or independent contractors have inadvertently or otherwise used or disclosed intellectual property, including trade secrets or other proprietary information, of any of our employee's former employer or other third parties. Litigation may be necessary to defend against these claims. If we fail in defending any such claims, in addition to paying monetary damages, we may lose valuable intellectual property rights or personnel, which could adversely impact our business. Even if we are successful in defending against such claims, litigation could result in substantial costs and be a distraction to management and other employees.

We may be subject to claims challenging the inventorship or ownership of our patents and other intellectual property.

We may be subject to claims that former employees, collaborators or other third parties have an ownership interest in our patents or other intellectual property. We may have potential ownership disputes arising, for example, from conflicting obligations of consultants, collaborators or others who are involved in developing our product candidates. Litigation may be necessary to defend against these and other claims challenging inventorship or ownership. If we fail in defending any such claims, in addition to paying monetary damages, we may lose valuable intellectual property rights, such as exclusive ownership of, or right to use, valuable intellectual property. Such an outcome could have a material adverse effect on our business. Even if we are successful in defending against such claims, litigation could result in substantial costs and be a distraction to management and other employees.

Changes in U.S. patent law could diminish the value of patents in general, thereby impairing our ability to protect our products.

As is the case with other biotechnology companies, our success is heavily dependent on intellectual property, particularly patents. Obtaining and enforcing patents in the biotechnology industry involve both technological and legal complexity, and therefore obtaining and enforcing biotechnology patents is costly, time-consuming and inherently uncertain. In addition, the United States has recently enacted and is currently implementing wide-ranging patent reform legislation. Recent U.S. Supreme Court rulings have

narrowed the scope of patent protection available in certain circumstances and weakened the rights of patent owners in certain situations. In addition to increasing uncertainty with regard to our ability to obtain patents in the future, this combination of events has created uncertainty with respect to the value of patents, once obtained. Depending on decisions by the U.S. Congress, the federal courts and the U.S. PTO, the laws and regulations governing patents could change in unpredictable ways that would weaken our ability to obtain new patents or to enforce our existing patents and patents that we might obtain in the future.

We have not yet registered trademarks for a commercial trade name for Toca 511 & Toca FC, and failure to secure such registrations could adversely affect our business.

We have not yet developed a proprietary name for our products nor registered trademarks for a commercial trade name for Toca 511 & Toca FC. During trademark registration proceedings, we may receive rejections. Although we would be given an opportunity to respond to those rejections, we may be unable to overcome such rejections. In addition, in the U.S. PTO and in comparable agencies in many foreign jurisdictions, third parties are given an opportunity to oppose pending trademark applications and to seek to cancel registered trademarks. Opposition or cancellation proceedings may be filed against our trademarks, and our trademarks may not survive such proceedings. Moreover, any name we propose to use with our product candidates in the United States must be approved by the FDA, regardless of whether we have registered it, or applied to register it, as a trademark. The FDA typically conducts a review of proposed product names, including an evaluation of potential for confusion with other product names. If the FDA objects to any of our proposed proprietary product names, we may be required to expend significant additional resources in an effort to identify a suitable substitute name that would qualify under applicable trademark laws, not infringe the existing rights of third parties and be acceptable to the FDA.

We may not be able to protect our intellectual property rights throughout the world.

Filing, prosecuting and defending patents on product candidates in all countries throughout the world would be prohibitively expensive, and our intellectual property rights in some countries outside the United States can be less extensive than those in the United States. In addition, the laws of some foreign countries do not protect intellectual property rights to the same extent as federal and state laws in the United States. Consequently, we may not be able to prevent third parties from practicing our inventions in all countries outside the United States, or from selling or importing products made using our inventions in and into the United States or other jurisdictions. Competitors may use our technologies in jurisdictions where we have not obtained patent protection to develop their own products and further, may export otherwise infringing products to territories where we have patent protection, but enforcement is not as strong as that in the United States. These products may compete with our products and our patents or other intellectual property rights may not be effective or sufficient to prevent them from competing.

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

Risks related to ownership of our common stock

The market price of our common stock may be highly volatile, and you could lose all or part of your investment.

The market price of our common stock is likely to be volatile. Our stock price could be subject to wide fluctuations in response to a variety of factors, including the following:

- adverse results or delays in preclinical or clinical trials;
- reports of adverse events in other gene therapy products or clinical trials of such products;
- inability to obtain additional funding;
- any delay in filing an IND or BLA for any of our product candidates and any adverse development or perceived adverse development with respect to the FDA's review of that IND or BLA;
- failure to develop successfully and commercialize our product candidates;
- failure to maintain our existing strategic collaboration or enter into new collaborations;

- failure by us or our licensors and strategic collaboration partners to prosecute, maintain or enforce our intellectual property rights;
- changes in laws or regulations applicable to future products;
- inability to obtain adequate product supply for our product candidates or the inability to do so at acceptable prices;
- adverse regulatory decisions;
- introduction of new products, services or technologies by our competitors;
- changes in the structure of healthcare payment systems;
- failure to meet or exceed financial projections we may provide to the public;
- failure to meet or exceed the financial projections of the investment community;
- the perception of the pharmaceutical industry by the public, legislatures, regulators and the investment community;
- announcements of significant acquisitions, strategic partnerships, joint ventures or capital commitments by us, our strategic collaboration partners or our competitors;
- disputes or other developments relating to proprietary rights, including patents, litigation matters and our ability to obtain patent protection for our technologies;
- additions or departures of key scientific or management personnel;
- significant lawsuits, including patent or stockholder litigation;
- changes in the market valuations of similar companies;
- sales of our common stock by us or our stockholders in the future; and
- trading volume of our common stock.

In addition, companies trading in the stock market in general, and the Nasdaq Global Select Market in particular, have experienced extreme price and volume fluctuations that have often been unrelated or disproportionate to the operating performance of these companies. Broad market and industry factors may negatively affect the market price of our common stock, regardless of our actual operating performance.

Unstable market and economic conditions may have serious adverse consequences on our business, financial condition and stock price.

From time to time, global credit and financial markets have experienced extreme volatility and disruptions, including severely diminished liquidity and credit availability, declines in consumer confidence, declines in economic growth, increases in unemployment rates and uncertainty about economic stability. Our general business strategy may be adversely affected by any such economic downturn, volatile business environment and continued unpredictable and unstable market conditions. If the equity and credit markets deteriorate it may make any necessary debt or equity financing more difficult to complete, more costly, and more dilutive. Failure to secure any necessary financing in a timely manner and on favorable terms could have a material adverse effect on our growth strategy, financial performance and stock price and could require us to delay or abandon clinical development plans. In addition, there is a risk that one or more of our current service providers, manufacturers and other partners may not survive an economic down-turn, which could directly affect our ability to attain our operating goals on schedule and on budget.

We do not intend to pay dividends on our common stock so any returns will be limited to the value of our stock.

We have never declared or paid any cash dividends on our common stock. We currently anticipate that we will retain future earnings for the development, operation and expansion of our business and do not anticipate declaring or paying any cash dividends for the foreseeable future, including due to limitations that are currently imposed by our Loan Agreement. Any return to stockholders will therefore be limited to the appreciation of their stock.

We are an emerging growth company, and we cannot be certain if the reduced reporting requirements applicable to emerging growth companies will make our common stock less attractive to investors.

We are an emerging growth company, as defined in the Jumpstart Our Business Startups Act, or JOBS Act. For as long as we continue to be an emerging growth company, we may take advantage of exemptions from various reporting requirements that are applicable to other public companies that are not emerging growth companies, including not being required to comply with the auditor attestation requirements of Section 404 of the Sarbanes-Oxley Act of 2002, as amended, or the Sarbanes-Oxley Act, reduced disclosure obligations regarding executive compensation in our periodic reports and proxy statements and exemptions from the

requirements of holding nonbinding advisory votes on executive compensation and stockholder approval of any golden parachute payments not previously approved. We could be an emerging growth company for up to five years following the year in which we completed our initial public offering, although circumstances could cause us to lose that status earlier. We will remain an emerging growth company until the earlier of (1) the last day of the fiscal year (a) following the fifth anniversary of the completion of our initial public offering (i.e. December 31, 2022), (b) in which we have total annual gross revenue of at least $1.07 billion or (c) in which we are deemed to be a large accelerated filer, which requires the market value of our common stock that is held by non-affiliates to exceed $700 million as of the prior June 30th, and (2) the date on which we have issued more than $1 billion in non-convertible debt during the prior three-year period.

Even after we no longer qualify as an emerging growth company, we may still qualify as a "smaller reporting company" which would allow us to take advantage of many of the same exemptions from disclosure requirements including not being required to comply with the auditor attestation requirements of Section 404 of the Sarbanes-Oxley Act and reduced disclosure obligations regarding executive compensation in our periodic reports and proxy statements. We cannot predict if investors will find our common stock less attractive because we may rely on these exemptions. If some investors find our common stock less attractive as a result, there may be a less active trading market for our common stock and our stock price may be more volatile.

Under the JOBS Act, emerging growth companies can also delay adopting new or revised accounting standards until such time as those standards apply to private companies. We have irrevocably elected not to avail ourselves of this exemption from new or revised accounting standards and, therefore, will be subject to the same new or revised accounting standards as other public companies that are not emerging growth companies. As a result, changes in rules of U.S. generally accepted accounting principles or their interpretation, the adoption of new guidance or the application of existing guidance to changes in our business could significantly affect our financial position and results of operations.

We will incur significant increased costs as a result of operating as a public company, and our management will be required to devote substantial time to existing and new compliance initiatives.

As a public company, we incur significant legal, accounting and other expenses that we did not incur as a private company. We are subject to the reporting requirements of the Securities Exchange Act of 1934, as amended, or the Exchange Act, which require, among other things, that we file with the SEC annual, quarterly and current reports with respect to our business and financial condition. In addition, the Sarbanes-Oxley Act, as well as rules subsequently adopted by the SEC and the Nasdaq Global Select Market to implement provisions of the Sarbanes-Oxley Act, impose significant requirements on public companies, including requiring establishment and maintenance of effective disclosure and financial controls and changes in corporate governance practices. Further, in July 2010, the Dodd-Frank Wall Street Reform and Consumer Protection Act, or the Dodd-Frank Act, was enacted. There are significant corporate governance and executive compensation related provisions in the Dodd-Frank Act that require the SEC to adopt additional rules and regulations in these areas such as "say on pay" and proxy access. Recent legislation permits emerging growth companies to implement many of these requirements over a longer period and up to five years from the pricing of our initial public offering. We intend to take advantage of this legislation but cannot guarantee that we will not be required to implement these requirements sooner than budgeted or planned and thereby incur unexpected expenses. Stockholder activism, the current political environment and the current level of government intervention and regulatory reform may lead to substantial new regulations and disclosure obligations, which may lead to additional compliance costs and impact the manner in which we operate our business in ways we cannot currently anticipate.

We expect the rules and regulations applicable to public companies to continue to result in substantial legal and financial compliance costs and to make some activities more time-consuming and costly. If these requirements divert the attention of our management and personnel from other business concerns, they could have a material adverse effect on our business, financial condition and results of operations. These costs could decrease our net income or increase our net loss, and may require us to reduce costs in other areas of our business or increase the prices of our products or services. For example, these rules and regulations could make it more difficult and more expensive for us to obtain director and officer liability insurance and we may be required to incur substantial costs to maintain the same or similar coverage. We cannot predict or estimate the amount or timing of additional costs we may incur to respond to these requirements. The impact of these requirements could also make it more difficult for us to attract and retain qualified persons to serve on our board of directors, our board committees or as executive officers.

Sales of a substantial number of shares of our common stock in the public market could cause our stock price to fall.

If our existing stockholders sell, or indicate an intention to sell, substantial amounts of our common stock in the public market, the market price of our common stock could decline. We had 23,019,097 shares of common stock outstanding as of February 22, 2019. We are unable to predict the effect that sales may have on the prevailing market price of our common stock.

Sales of our common stock by current stockholders may make it more difficult for us to sell equity or equity-related securities in the future at a time and price that we deem reasonable or appropriate, and make it more difficult for other stockholders to sell shares of our common stock. In addition, as of December 31, 2018, 3,995,148 shares of common stock that are either subject to outstanding options, reserved for future issuance under our equity incentive plans or subject to outstanding warrants will become eligible for sale in the public market to the extent permitted by the provisions of various vesting schedules and Rule 144 and Rule 701 under the Securities Act. If these additional shares of common stock are sold, or if it is perceived that they will be sold, in the public market, the market price of our common stock could decline.

Future sales and issuances of our common stock or rights to purchase common stock, including pursuant to our equity incentive plans, could result in additional dilution of the percentage ownership of our stockholders and could cause our stock price to fall.

Additional capital will be needed in the future to continue our planned operations. To the extent we raise additional capital by issuing equity securities, our stockholders may experience substantial dilution. We may sell common stock, convertible securities or other equity securities in one or more transactions at prices and in a manner we determine from time to time. If we sell common stock, convertible securities or other equity securities in more than one transaction, investors may be materially diluted by subsequent sales. These sales may also result in material dilution to our existing stockholders, and new investors could gain rights superior to our existing stockholders.

In November 2018, we entered into the ATM facility with Citigroup, pursuant to which we may sell and issue shares of our common stock having an aggregate offering price of up to $30.0 million from time to time through Citigroup, as our sales agent. As of December 31, 2018, we have not sold any shares of our common stock under the ATM facility.

Pursuant to our 2017 Equity Incentive Plan, or 2017 Plan, our management is authorized to grant stock options to our employees, directors and consultants. The number of shares of our common stock reserved for issuance under our 2017 Plan will automatically increase on January 1 of each year through and including January 1, 2027, by 4% of the total number of shares of our capital stock outstanding on December 31 of the preceding calendar year, or a lesser number of shares determined by our board of directors. Additionally, the number of shares of our common stock reserved for issuance under our 2017 Employee Stock Purchase Plan, or the ESPP, will automatically increase on January 1 of each year through and including January 1, 2027, by the lesser of 1% of the total number of shares of our capital stock outstanding on December 31 of the preceding calendar year, 300,000 shares or a lesser number of shares determined by our board of directors. Unless our board of directors elects not to increase the number of shares available for future grant each year under the 2017 Plan and the ESPP, our stockholders may experience additional dilution, which could cause our stock price to fall.

We have broad discretion in the use of working capital and may not use it effectively.

Our management will have broad discretion in the application of working capital, and stockholders do not have the opportunity to assess whether working capital is being used appropriately. Because of the number and variability of factors that will determine our use of our working capital, its ultimate use may vary substantially from its currently intended use. Management might not apply working capital in ways that ultimately increase stockholder value. We intend to use our working capital to fund our Phase 3 clinical trial of Toca 511 & Toca FC in recurrent HGG, manufacturing scale-up and validation for Toca 511 & Toca FC, the other ongoing and planned clinical development and regulatory activities for Toca 511 & Toca FC, commercial scale up efforts, and for other general corporate purposes. Failure by us to apply working capital effectively could harm our business. Pending its use, we may invest our working capital in short-term, investment-grade, interest-bearing securities. These investments may not yield a favorable return to our stockholders. If we do not invest or apply our working capital in ways that enhance stockholder value, we may fail to achieve expected financial results, which could cause our stock price to decline.

Comprehensive tax reform could adversely affect our business and financial condition.

On December 22, 2017, U.S. federal income tax legislation was signed into law (H.R. 1, "An Act to provide for reconciliation pursuant to titles II and V of the concurrent resolution on the budget for fiscal year 2018"), informally titled the Tax Cuts and Jobs Act, or Tax Act, that significantly revised the Internal Revenue Code of 1986, as amended, or IRC. The Tax Act, among other things, contained significant changes to corporate taxation, including reduction of the corporate tax rate from a top marginal rate of 35% to a flat rate of 21%, limitation of the tax deduction for interest expense to 30% of adjusted earnings, except for certain small businesses, limitation of the deduction for net operating losses to 80% of current year taxable income and elimination of net operating loss carrybacks, one time taxation of offshore earnings at reduced rates regardless of whether they are repatriated, elimination of U.S. tax on foreign earnings, subject to certain important exceptions, immediate deductions for certain new investments instead of deductions for depreciation expense over time and modification or repeal of many business deductions and credits, including reduction of the business tax credit for certain clinical testing expenses incurred in the testing of certain drugs for rare diseases or conditions. Notwithstanding the reduction in the corporate income tax rate, the overall impact of the Tax Act is uncertain, and our business and financial condition could be adversely affected. In addition, it is unknown if and to what extent various states will conform to the Tax Act. The impact of the Tax Act on holders of our common stock is likewise uncertain and could be adverse. We urge our stockholders to consult with their legal and tax advisors with respect to the Tax Act and the potential tax consequences of investing in or holding our common stock.

Our ability to use our net operating loss carryforwards and certain other tax attributes may be limited.

As of December 31, 2018, we had federal net operating losses of $174.1 million, of which $136.6 million begin to expire in 2028 unless previously utilized and $37.5 million do not expire but are limited to 80% of taxable income in a given year. As of December 31, 2018, we had California net operating loss carryforwards of $76.1 million that begin to expire in 2028 unless previously utilized. If these net operating loss carryforwards expire unused, they will be unavailable to offset future income and reduce future income tax liabilities. In addition, under the Tax Act, federal net operating losses incurred in 2018 and in future years may be carried forward indefinitely, but the deductibility of such federal net operating losses is limited. It is uncertain if and to what extent various states will conform to the Tax Act. Under Sections 382 and 383 of the IRC, if a corporation undergoes an "ownership change," generally defined as a cumulative change in its equity ownership by "5-percent shareholders" of greater than 50 percentage points (by value) over a three-year period, the corporation's ability to use its pre-change net operating loss carryforwards, or NOLs, and certain other pre-change tax attributes (such as research tax credits) to offset its post-change taxable income and taxes, as applicable, may be limited. We have completed public offerings and multiple other rounds of financing since our inception which may have resulted in an ownership change or could result in one or more ownership changes in the future. As of December 31, 2018, we have not completed a Section 382 and 383 analysis regarding any limitations on our NOLs and research and development credit carryforwards and such limitations could be significant. We may also experience ownership changes in the future as a result of subsequent shifts in our stock ownership. As a result, our ability to use our NOLs and research and development credit carryforwards to offset our U.S. federal taxable income and taxes, as applicable, may be subject to limitations, which could potentially result in increased future tax liability to us. In addition, at the state level, similar rules may apply and there may be periods during which the use of NOLs is suspended or otherwise limited, which could accelerate or permanently increase state taxes owed.

If securities or industry analysts do not publish research or publish inaccurate or unfavorable research about our business, our stock price and trading volume could decline.

The trading market for our common stock will depend in part on the research and reports that securities or industry analysts publish about us or our business. If one or more of the analysts who covers us downgrades our stock or publishes inaccurate or unfavorable research about our business, our stock price may decline. If one or more of these analysts ceases coverage of our company or fails to publish reports on us regularly, demand for our stock could decrease, which might cause our stock price and trading volume to decline.

Provisions in our amended and restated certificate of incorporation and amended and restated bylaws, as well as provisions of Delaware law, could make it more difficult for a third party to acquire us or increase the cost of acquiring us, even if doing so would benefit our stockholders or remove our current management.

Our amended and restated certificate of incorporation, amended and restated bylaws and Delaware law contain provisions that may have the effect of delaying or preventing a change in control of us or changes in our management. Our amended and restated certificate of incorporation and amended and restated bylaws, include provisions that:

- permit our board of directors to issue up to 10,000,000 shares of preferred stock, with any rights, preferences and privileges as they may designate (including the right to approve an acquisition or other change in our control);
- provide that the authorized number of directors may be changed only by resolution of the board of directors;
- provide that the board of directors or any individual director may only be removed with cause and the affirmative vote of the holders of at least 66-2/3% of the voting power of all of our then outstanding common stock;
- provide that all vacancies, including newly created directorships, may, except as otherwise required by law, be filled by the affirmative vote of a majority of directors then in office, even if less than a quorum;
- divide our board of directors into three classes;
- require that any action to be taken by our stockholders must be effected at a duly called annual or special meeting of stockholders and not be taken by written consent;
- provide that stockholders seeking to present proposals before a meeting of stockholders or to nominate candidates for election as directors at a meeting of stockholders must provide notice in writing in a timely manner and also specify requirements as to the form and content of a stockholder's notice;
- do not provide for cumulative voting rights (therefore allowing the holders of a majority of the shares of common stock entitled to vote in any election of directors to elect all of the directors standing for election, if they should so choose);
- provide that special meetings of our stockholders may be called only by the chairman of the board, our Chief Executive Officer or by the board of directors pursuant to a resolution adopted by a majority of the total number of authorized directors; and

- provide that the Court of Chancery of the State of Delaware will be the sole and exclusive forum for (i) any derivative action or proceeding brought on our behalf, (ii) any action asserting a claim of breach of a fiduciary duty owed by any of our directors or officers to us or our stockholders, (iii) any action asserting a claim against us arising pursuant to any provision of the Delaware General Corporation Law or our certificate of incorporation or bylaws, or (iv) any action asserting a claim against us governed by the internal affairs doctrine.

These provisions, alone or together, could delay or prevent hostile takeovers and changes in control or changes in our management.

In addition, because we are incorporated in Delaware, we are governed by the provisions of Section 203 of the Delaware General Corporation Law, which limits the ability of stockholders owning in excess of 15% of our outstanding voting stock to merge or combine with us.

Any provision of our amended and restated certificate of incorporation or amended and restated bylaws or Delaware law that has the effect of delaying or deterring a change in control could limit the opportunity for our stockholders to receive a premium for their shares of our common stock, and could also affect the price that some investors are willing to pay for our common stock.

Our amended and restated certificate of incorporation and amended and restated bylaws provide that the Court of Chancery of the State of Delaware is the sole and exclusive forum for substantially all disputes between us and our stockholders, which could limit our stockholders' ability to obtain a favorable judicial forum for disputes with us or our directors, officers or employees.

Our amended and restated certificate of incorporation and amended and restated bylaws provide that the Court of Chancery of the State of Delaware is the sole and exclusive forum for (i) any derivative action or proceeding brought on our behalf; (ii) any action asserting a breach of fiduciary duty owed by any of our directors, officers or other employees to us or our stockholders; (iii) any action asserting a claim against us or any of our directors, officers or other employees arising pursuant to the Delaware General Corporation Law, our amended and restated certificate of incorporation or our amended and restated bylaws; or (iv) any action asserting a claim against us or any of our directors, officers or other employees that is governed by the internal affairs doctrine. The choice of forum provision may limit a stockholder's ability to bring a claim in a judicial forum that it finds favorable for disputes with us or our directors, officers or other employees, which may discourage such lawsuits against us and our directors, officers and other employees. Alternatively, if a court were to find the choice of forum provision contained in our amended and restated certificate of incorporation and amended and restated bylaws to be inapplicable or unenforceable in an action, we may incur additional costs associated with resolving such action in other jurisdictions, which could adversely affect our business and financial condition.

Item 1B. Unresolved Staff Comments.

None.

Item 2. Properties.

As of December 31, 2018, we leased a total of approximately 39,000 square feet of laboratory and office space located at 4242 Campus Point Court, Suite 500, San Diego, California, 92121. We believe our existing facility is adequate to meet our business requirements for the foreseeable future and is sufficient and suitable for the conduct of our business.

Item 3. Legal Proceedings.

None.

Item 4. Mine Safety Disclosures.

Not applicable.

PART II

Item 5. Market for Registrant's Common Equity, Related Stockholder Matters and Issuer Purchases of Equity Securities.

Market Information

Our common stock began trading on the Nasdaq Global Select Market under the symbol "TOCA" on April 13, 2017. Prior to that date, there was no public trading market for our common stock.

Holders of Record

As of February 22, 2019, there were approximately 379 stockholders of record of our common stock. The actual number of stockholders is greater than this number of record holders and includes stockholders who are beneficial owners but whose shares are held in street name by brokers and other nominees. This number of holders of record also does not include stockholders whose shares may be held in trust or by other entities.

Dividend Policy

We have never declared or paid cash dividends on our capital stock. We currently intend to retain all available funds and any future earnings for use in the operation of our business and do not anticipate paying any dividends on our common stock in the foreseeable future. Any future determination to declare dividends will be made at the discretion of our board of directors and will depend on, among other factors, our financial condition, operating results, capital requirements, contractual restrictions, general business conditions and other factors that our board of directors may deem relevant. In addition, the terms of our Loan Agreement prohibit us from paying cash dividends.

Securities Authorized for Issuance Under Our Equity Compensation Plans

Information regarding securities authorized for issuance under our equity compensation plans is incorporated herein by reference to Item 12, "Security Ownership of Certain Beneficial Owners and Management and Related Stockholder Matters" of Part III of this Annual Report on Form 10-K.

Use of Proceeds

On April 12, 2017, our Registration Statement on Form S-1 (file No. 333-216574) was declared effective by the SEC for our initial public offering of common stock. We issued 9,775,000 shares of common stock at an offering price of $10.00 per share for gross proceeds of $97.8 million. After deducting underwriting discounts, commissions and offering costs incurred by us of $10.8 million, the net proceeds from the offering were $86.9 million. The offering was completed on April 19, 2017. The joint bookrunning managers for the offering were Leerink Partners LLC, Evercore Group L.L.C. and Stifel, Nicolaus & Company, Incorporated. No offering costs were paid or are payable, directly or indirectly, to our directors or officers, to persons owning 10% or more of any class of our equity securities, or to any of our affiliates.

There has been no material change in the expected use of the net proceeds from our initial public offering as described in our final prospectus filed with the SEC on April 13, 2017. As of December 31, 2018, we have used $54.2 million of the net proceeds from the offering. Pending such uses, we plan to continue investing the unused proceeds from this offering in fixed, non-speculative income instruments.

Purchases of Equity Securities by the Issuer and Affiliated Purchasers

None.

Item 6. Selected Financial Data.

The selected financial data set forth below is derived from our audited financial statements, including the balance sheets at December 31, 2018 and 2017 and the related statements of operations for each of the years ended December 31, 2018, 2017 and 2016 and related notes appearing elsewhere in this Annual Report. The following selected financial data should be read in conjunction with "Management's Discussion and Analysis of Financial Condition and Results of Operations," and our financial statements and the related notes thereto, each included elsewhere in this Annual Report on Form 10-K. The selected financial data in this section are not intended to replace our financial statements and the related notes. Our historical results are not necessarily indicative of our future results.

	Years Ended December 31,		
	2018	2017	2016
	(in thousands, except share and per share data)		
Statements of Operations Data			
License revenue	$ 18,036	$ 41	$ 49
Operating expenses:			
Research and development	51,080	29,113	27,218
General and administrative	12,809	8,556	4,521
Total operating expenses	63,889	37,669	31,739
Loss from operations	(45,853)	(37,628)	(31,690)
Other income (expense), net:			
Interest income	1,534	595	215
Interest expense	(2,937)	(1,932)	(2,052)
Change in fair value of preferred stock warrants	—	37	50
Loss before income taxes	(47,256)	(38,928)	(33,477)
Income tax expense	1,699	1	1
Net loss	$ (48,955)	$ (38,929)	$ (33,478)
Other comprehensive income (loss):			
Net unrealized gain (loss) on investments	11	(34)	58
Comprehensive loss	$ (48,944)	$ (38,963)	$ (33,420)
Net loss per common share, basic and diluted	$ (2.44)	$ (2.66)	$ (15.22)
Weighted-average number of common shares outstanding, basic and diluted	20,059,541	14,607,609	2,199,964

	As of December 31,		
	2018	2017	2016
		(in thousands)	
Balance Sheet Data:			
Cash, cash equivalents and marketable securities	$ 96,086	$ 88,725	$ 31,245
Working capital	81,214	73,299	18,079
Total assets	103,081	92,073	35,351
Notes payable, current portion	—	7,200	7,200
Notes payable, net of current portion	26,201	3,625	10,241
Deferred rent, net of current portion	2,201	—	—
Preferred stock warrant liabilities	—	—	126
Accumulated deficit	(215,884)	(166,929)	(128,000)
Total stockholders' equity (deficit)	58,145	71,082	(124,417)

Item 7. Management's Discussion and Analysis of Financial Condition and Results of Operations.

You should read the following discussion and analysis of our financial condition and results of operations together with the section entitled "Selected Financial Data" and our financial statements and related notes appearing elsewhere in this Annual Report on Form 10-K. This discussion and analysis contains forward-looking statements based upon current expectations that involve risks and uncertainties. Our actual results may differ materially from those anticipated in these forward-looking statements as a result of various factors, including those discussed in the section entitled "Risk Factors" and in other parts of this Annual Report on Form 10-K. Please also see the section entitled "Special Note Regarding Forward-Looking Statements."

Overview

We are a clinical-stage, cancer-selective gene therapy company focused on developing first-in-class, broadly-applicable product candidates designed to activate a patient's immune system against their own cancer. Our cancer-selective gene therapy platform is built on retroviral replicating vectors, which are designed to selectively deliver therapeutic genes into the DNA of cancer cells. Our gene therapy approach is designed to fight cancer through immunotherapeutic mechanisms of action without the autoimmune toxicities commonly experienced with other immunotherapies.

We are developing our lead product candidate, Toca 511 (vocimagene amiretrorepvec) & Toca FC (extended-release flucytosine), initially for the treatment of recurrent high grade glioma, or HGG, a brain cancer with limited treatment options, low survival rates and, therefore, a significant unmet medical need. We are conducting a randomized, controlled Phase 3 clinical trial of Toca 511 & Toca FC in patients with recurrent HGG (Toca 5), which is designed to serve as a registrational trial. Enrollment was completed for this clinical trial in September 2018. In February 2017, the U.S. Food and Drug Administration, or FDA, granted Toca 511 & Toca FC Breakthrough Therapy Designation for the treatment of patients with recurrent HGG and in June 2017 the European Medicines Agency, or EMA, granted Toca 511 Priority Medicines, or PRIME, Designation for the treatment of patients with HGG. Breakthrough Therapy Designation indicates that preliminary clinical evidence demonstrates the drug may have substantial improvement on one or more clinically significant endpoints over available therapy. PRIME Designation indicates that there is a potential to benefit patients with unmet medical needs based on early clinical data. We also have Fast Track Designation (which may lead to priority review of new products that treat serious diseases or conditions and demonstrate the potential to address an unmet medical need) from the FDA for Toca 511 & Toca FC for the treatment of recurrent HGG. We also received Orphan-Drug Designation from the FDA for the treatment of malignant glioma in addition to glioblastoma multiforme. Orphan-Drug Designation is a designation for a product that treats a rare disease or condition and which, if the product receives the first FDA approval for that disease or condition, may result in a period of regulatory exclusivity, subject to some exceptions. The Committee for Orphan Medicinal Products of the EMA has designated both flucytosine and vocimagene amiretrorepvec as orphan medicinal products indicated for the treatment of glioma. The EMA provides several benefits to drug developers for developing drugs for orphan diseases.

In April 2018, we entered into a license agreement, or License Agreement, with Beijing Apollo Venus Biomedical Technology Limited and ApolloBio Corp., or collectively ApolloBio, which became effective in July 2018, pursuant to which we granted to ApolloBio an exclusive license to develop and commercialize Toca 511 & Toca FC within the greater China region, including mainland China, Hong Kong, Macao and Taiwan, or the Licensed Territory. Under the License Agreement, we received an aggregate upfront payment of $16.0 million and we are eligible to receive up to a total of $111.0 million upon achievement of specified development and commercial milestones. In addition, we are also eligible for low double-digit tiered royalty payments based on annual net sales of licensed products in the Licensed Territory, subject to reduction under specified circumstances. In September 2018, we earned a $2.0 million development milestone payment upon completion of the planned enrollment of 380 patients in the Toca 5 clinical trial.

We do not have any products approved for sale and have not generated any revenue from product sales. We have funded our operations primarily through the private placement of our convertible preferred stock, from which we received net proceeds of $131.4 million and our initial public offering in April 2017, from which we received net proceeds of $86.9 million and our public offering in December 2018 from which we received net proceeds of $28.0 million. We have also received $44.0 million in net proceeds from term loans, $15.7 million in net proceeds from upfront and milestone payments under our license and collaboration agreements, $10.9 million from the issuance of our convertible promissory notes payable, and $2.6 million from private and federal grants.

Since our inception in August 2007, we have devoted substantially all of our efforts to developing our gene therapy platform and our lead product candidate, Toca 511 & Toca FC. We have never been profitable and have incurred significant operating losses in each year since our inception. We had an accumulated deficit of $215.9 million as of December 31, 2018. Substantially all of our net losses resulted from costs incurred in connection with our research, preclinical, clinical, product, regulatory and business development activities, as well as raising capital and building our infrastructure.

We expect to continue to incur significant expenses and increasing net operating losses for at least the next several years. We expect our expenses will increase substantially in connection with our ongoing activities as we continue to develop and seek regulatory approval of our product candidates and operate as a public company. To fund further operations, we will need to raise additional capital.

Accordingly, we will seek to fund our operations through equity and/or debt financings. We may also consider new collaborations or selectively partnering our technology or programs. However, we may be unable to raise additional funds or enter into such other arrangements when needed on favorable terms or at all. In addition, subject to limited exceptions, our Loan Agreement (as defined below) also prohibits us from incurring indebtedness without the prior written consent of the lenders. Our failure to raise capital or enter into such other arrangements as and when needed would have a negative impact on our financial condition and our ability to develop our product candidates.

ATM Facility

In November 2018, we entered into an Equity Distribution Agreement with Citigroup Global Markets Inc., or Citigroup, pursuant to which we may sell and issue shares of our common stock having an aggregate offering price of up to $30,000,000 from time to time through Citigroup, as our sales agent, or the ATM facility. As of December 31, 2018, we have not sold any shares of our common stock under the ATM facility.

Public Offering

In December 2018, we completed a public offering in which we sold an aggregate of 3,000,000 shares of common stock at a price of $10.00 per share. Net proceeds from the public offering, after deducting underwriting discounts, commissions and offering expenses, were approximately $28.0 million.

Financial Operations Overview

Revenue

We currently have no products approved for sale, and have not generated any revenues from the sale of products. We have not submitted any product candidate for regulatory approval. Our revenue has been derived from our license and collaboration arrangement we entered into with Siemens Healthcare Diagnostics Inc., or Siemens, in 2011 under which we received a nonrefundable, non-creditable, lump-sum, upfront license payment of $0.5 million for our sublicense to Siemens of certain diagnostic assay technology and the License Agreement with ApolloBio, under which we received net proceeds of $15.2 million which was comprised of a $16.0 million up-front payment and a $2.0 million development milestone payment less $1.7 million in foreign income taxes and $1.1 million in certain foreign non-income taxes. As of December 31, 2018, $18.0 million in revenue was recognized under the License Agreement.

In the future, we may generate revenue from a combination of product sales, royalties and milestones in connection with our Siemens agreement, the License Agreement and any future marketing and distribution arrangements and other collaborations, strategic alliances and license arrangements, or a combination of these approaches. However, we do not expect to receive additional revenues unless and until we receive regulatory approval for product candidates or potentially enter into other collaboration agreements. We expect that any revenue we generate will fluctuate from quarter to quarter and year to year as a result of the timing and amount of license fees, milestone and other payments, and the amount and timing of payments that we receive upon the sale of our products, to the extent any are successfully commercialized. If we fail to complete the development of our product candidates in a timely manner or obtain regulatory approval of them, our ability to generate future revenue, and our results of operations and financial position, would be materially adversely affected.

Research and Development Expenses

Research and development expenses consist primarily of salaries and related expenses for personnel, including non-cash stock-based compensation costs, preclinical costs, clinical trial costs, costs related to acquiring and manufacturing clinical trial materials, contract services, facilities costs, overhead costs and depreciation. These activities also include research and development related to our gene therapy platform development. All research and development costs are expensed as incurred.

We cannot determine with certainty the duration and completion costs of the current or future clinical trials of our product candidates, or if, when or to what extent we will generate revenues from the commercialization and sale of any of our product candidates that obtain regulatory approval. We may never succeed in achieving regulatory approval for any of our product candidates. The duration, costs and timing of clinical trials and development of our product candidates will depend on a variety of factors, including:

- per patient trial costs;
- the number of patients that participate in the trials;
- the number of sites included in the trials;
- the countries in which the trials are conducted;
- the length of time required to enroll eligible patients;
- the drop-out or discontinuation rates of patients;
- the potential for additional safety monitoring or other clinical trials requested by regulatory agencies;
- significant and changing government regulation; and
- the timing and receipt of any regulatory approvals.

A change in the outcome of any of these variables with respect to the development of a product candidate could mean a significant change in the costs and timing associated with the development of that product candidate. For example, if the FDA or another regulatory authority were to require us to conduct clinical trials beyond those that we currently anticipate will be required for the completion of clinical development of a product candidate or if we experience significant delays in enrollment in any of our clinical trials, we could be required to expend significant additional financial resources and time on the completion of clinical development. In addition, the probability of success for each product candidate will depend on numerous factors, including competition, manufacturing capability and commercial viability. We will determine which programs to pursue and how much to fund each program in response to the scientific and clinical success of each product candidate, as well as an assessment of each product candidate's commercial potential.

The following table sets forth our research and development expense by project for the years ended December 31, 2018, 2017 and 2016 (in thousands):

	Years Ended December 31,		
	2018	2017	2016
Toca 511 & Toca FC	$ 46,872	$ 27,471	$ 26,490
Vector technology	4,208	1,642	728
Total	$ 51,080	$ 29,113	$ 27,218

We expect our research and development expenses to increase for the foreseeable future as we scale up our clinical trial and manufacturing activities and seek regulatory approval of our product candidates.

General and Administrative Expenses

General and administrative expenses consist primarily of salaries and related expenses for personnel, including non-cash stock-based compensation costs and travel expenses for our employees in executive, operational, finance and business development functions. Other general and administrative expenses include facility-related costs, consulting fees, information technology, insurance, professional fees for accounting and legal services, expenses associated with obtaining and maintaining patents and costs associated with being a public company.

We anticipate that our general and administrative expenses will increase in the future as we increase our headcount to support our expanding research and development and potential commercialization of our product candidates. We also anticipate continued increases in expenses related to audit, legal, regulatory and tax-related services associated with maintaining compliance with exchange listing and SEC requirements, director and officer insurance premiums and investor relations costs associated with being a public company. Additionally, if we believe a regulatory approval of our lead product candidate appears likely, we anticipate an increase in payroll and related expenses as a result of our preparation for commercial operations, especially as it relates to establishing a sales force and other expenses related to the sale and marketing of our product candidates.

Interest Income

Interest income consists primarily of interest income earned on cash, cash equivalents and marketable securities.

Interest Expense

Interest expense consists primarily of stated interest and the amortization of related debt issuance costs incurred on the outstanding principal amount of our borrowings under our notes payable and convertible promissory notes payable.

Income tax expense

Income tax expense consists primarily of foreign income tax expense incurred related to our License Agreement with ApolloBio.

Critical Accounting Policies and Significant Judgments and Estimates

Our management's discussion and analysis of our financial condition and results of operations is based on our financial statements which we have prepared in accordance with generally accepted accounting principles in the United States. The preparation of these financial statements requires us to make estimates and assumptions that affect the reported amounts of assets and liabilities and disclosure of contingent assets and liabilities at the date of the financial statements, and the reported amounts of revenue and expenses during the reporting period. Actual results could differ from those estimates.

While our significant accounting policies are described in more detail in the Note 2 to our financial statements appearing at the end of this Annual Report on Form 10-K, we believe the following accounting policies to be most critical for fully understanding and evaluating our financial condition and results of operations.

Revenue Recognition

Revenue generally consists of license revenue with upfront payments and development milestones considered probable of achievement.

Revenue is recognized when control of the promised goods or services is transferred to our customers in an amount that reflects the consideration we expect to receive from our customers in exchange for those goods and services. This process involves identifying the contract with a customer, determining the performance obligations in the contract, determining the transaction price, allocating the contract price to the distinct performance obligations in the contract, and recognizing revenue when or as we satisfy the performance obligation(s).

At contract inception, we assess the goods and services promised within each contract and assess whether each promised good or service is distinct and determine that those are performance obligations. A performance obligation is considered distinct from other obligations in a contract when it provides a benefit to the customer either on its own or together with other resources that are readily available to the customer and is separately identified in the contract. We consider factors such as the research, manufacturing and commercialization capabilities of the collaboration partner and the availability of the associated expertise in the general marketplace. We consider a performance obligation satisfied once we have transferred control of a good or service to the customer, meaning the customer has the ability to use and obtain the benefit of the good or service. We recognize revenue for satisfied performance obligations only when we determine there are no uncertainties regarding payment terms or transfer of control.

Collaborative Arrangements

We enter into collaborative arrangements with partners that may include payment to us of one or more of the following: (i) license fees; (ii) payments related to the achievement of developmental, regulatory, or commercial milestones; and (iii) royalties on net sales of licensed products. Where a portion of non-refundable upfront fees or other payments received are allocated to continuing performance obligations under the terms of a collaborative arrangement, they are recorded as contract liabilities and recognized as revenue when (or as) the underlying performance obligation is satisfied.

As part of the accounting for these arrangements, we must develop estimates and assumptions that require judgment to determine the underlying stand-alone selling price for each performance obligation which determines how the transaction price is allocated among the performance obligation(s). The stand-alone selling price may include items such as forecasted revenues, development timelines, discount rates, and probabilities of technical and regulatory success. We evaluate each performance obligation to determine if it can be satisfied at a point in time or over time. In addition, variable consideration must be evaluated to determine if it is constrained and, therefore, excluded from the transaction price.

License Fees

If a license to our intellectual property is determined to be distinct from the other performance obligations identified in the arrangement, we recognize revenues from non-refundable, upfront fees allocated to the license when the license is transferred to the licensee and the licensee is able to use and benefit from the license. For licenses that are bundled with other promises, we utilize judgment to assess the nature of the combined performance obligation to determine whether the combined performance obligation is satisfied over time or at a point in time and, if over time, the appropriate method of measuring progress for purposes of recognizing revenue. We evaluate the measure of progress each reporting period and, if necessary, adjust the measure of performance and related revenue recognition. Any such adjustments are recorded on a cumulative catch-up basis, which would affect license, collaboration or other revenues and earnings in the period of adjustment.

Milestone Payments

At the inception of each arrangement that includes milestone payments (variable consideration), we evaluate whether the milestones are considered probable of being reached and estimate the amount to be included in the transaction price. If it is probable that a milestone event would occur at the inception of the arrangement, the associated milestone value is included in the transaction price. Milestone payments that are not within our control, such as regulatory approvals, are generally not considered probable of being achieved until those approvals are received. The transaction price is then allocated to each performance obligation on a relative stand-alone selling price basis, for which we recognize revenue as or when the performance obligations under the contract are satisfied. At the end of each reporting period, we evaluate the probability of achievement of such milestones and any related constraint(s), and if necessary, may adjust our estimate of the overall transaction price. Any such adjustments are recorded on a cumulative catch-up basis, which would affect license, collaboration or other revenues and earnings in the period of adjustment.

Royalties

For arrangements that include sales-based royalties, including milestone payments based on the level of sales, and for which the license is deemed to be the predominant item to which the royalties relate, we recognize revenue at the later of (i) when the related sales occur, or (ii) when the performance obligation to which some or all of the royalty has been allocated has been satisfied (or partially satisfied). To date, we have not recognized any royalty revenue resulting from our collaborative arrangements.

Clinical Trial Accruals

Expenses related to clinical studies are based on estimates of the services received and efforts expended pursuant to our contract arrangements. The financial terms of these agreements are subject to negotiation, vary from contract to contract and may result in uneven payment flows. There may be instances in which payments made to our service providers will temporarily exceed the level of services provided and result in a prepayment of the clinical expense. Payments under some of these contracts depend on factors such as the successful enrollment of patients, site initiation and the completion of clinical milestones. We make estimates of our accrued expenses as of each balance sheet date in its financial statements based on facts and circumstances known at that time. In accruing service fees, we estimate the time period over which services will be performed and the level of effort to be expended in each period. If the actual timing of the performance of services or the level of effort varies from our estimate, we adjust the accrual or prepaid expense balance accordingly. Historically, our estimated accrued liabilities have materially approximated actual expense incurred.

Recent Accounting Pronouncements

We have reviewed all recently issued standards and have determined that other than as disclosed in Note 2 to our financial statements included in this Annual Report on Form 10-K, such standards will not have a material impact on our financial statements or do not otherwise apply to our operations.

Results of Operations

Comparison of the Years Ended December 31, 2018 and 2017

The following table summarizes our results of operations for the years ended December 31, 2018 and 2017 (in thousands):

	Years Ended December 31,		Increase
	2018	2017	(Decrease)
License revenue	$ 18,036	$ 41	$ 17,995
Research and development expenses	51,080	29,113	21,967
General and administrative expenses	12,809	8,556	4,253
Interest income	1,534	595	939
Interest expense	(2,937)	(1,932)	(1,005)
Income tax expense	1,699	1	1,698

License revenue License revenue was $18.0 million for the year ended December 31, 2018 as compared to $41,000 for the year ended December 31, 2017, an increase of $18.0 million. Under the License Agreement with ApolloBio, we recognized a $16.0 million upfront payment and a $2.0 million development milestone payment for the year ended December 31, 2018.

Research and development expenses Research and development expenses were $51.1 million for the year ended December 31, 2018, as compared to $29.1 million for the year ended December 31, 2017. The increase of $22.0 million was primarily due to increases in manufacturing and clinical trial costs of $15.3 million to support our Phase 3 clinical trial which completed enrollment in September 2018 and increased personnel costs, including non-cash stock based compensation of $3.0 million due to an increase in headcount.

General and administrative expenses General and administrative expenses were $12.8 million for the year ended December 31, 2018, as compared to $8.6 million for the year ended December 31, 2017. The increase of $4.3 million was primarily due to increased personnel costs, including non-cash stock based compensation, of $1.0 million, a $1.1 million non-income tax expense related to the ApolloBio License Agreement and an increase in facility related expense due to our lab and office space lease which was signed in 2018 and increases in external service costs associated with the growth of our business and other costs associated with general business activities.

Interest income Interest income was $1.5 million for the year ended December 31, 2018, as compared to $0.6 million for the year ended December 31, 2017. The increase of $0.9 million was primarily due to our higher average cash balances earning interest at higher rates during 2018 compared to 2017.

Interest expense Interest expense was $2.9 million for the year ended December 31, 2018, as compared to $1.9 million for the year ended December 31, 2017 due to our increased debt principal balance and exit fees associated with refinancing our debt agreement during 2018.

Income tax expense Income tax expense of $1.7 million recorded for the year ended December 31, 2018 was due to foreign income tax expense paid in conjunction with our License Agreement with ApolloBio.

Comparison of the Years Ended December 31, 2017 and 2016

The following table summarizes our results of operations for the years ended December 31, 2017 and 2016 (in thousands):

	Years Ended December 31,		Increase
	2017	2016	(Decrease)
License revenue	$ 41	$ 49	$ (8)
Research and development expenses	29,113	27,218	1,895
General and administrative expenses	8,556	4,521	4,035
Interest income	595	215	380
Interest expense	(1,932)	(2,052)	120
Change in fair value of preferred stock warrants	37	50	(13)

License revenue License revenue was $41,000 for the year ended December 31, 2017 as compared to $49,000 for the year ended December 31, 2016, a decrease of $8,000.

Research and development expenses Research and development expenses were $29.1 million for the year ended December 31, 2017, as compared to $27.2 million for the year ended December 31, 2016. The increase of $1.9 million was primarily due to increased personnel costs to support our Phase 3 clinical trial.

General and administrative expenses General and administrative expenses were $8.6 million for the year ended December 31, 2017, as compared to $4.5 million for the year ended December 31, 2016. The increase of $4.1 million was primarily due to higher personnel costs to support increased operations activity as we conduct our Phase 3 clinical trial and costs associated with being a public company as we went public in April 2017.

Interest income Interest income was $0.6 million for the year ended December 31, 2017, as compared to $0.2 million for the year ended December 31, 2016. The increase of $0.4 million was primarily due to our higher average cash balances earning interest at higher rates during 2017 compared to 2016.

Interest Expense Interest expense was $1.9 million for the year ended December 31, 2017, as compared to $2.1 million for the year ended December 31, 2016 related to our outstanding debt.

Liquidity and Capital Resources

We have incurred significant losses and cumulative negative cash flows from operations since our inception. As of December 31, 2018, we had an accumulated deficit of $215.9 million and we anticipate that we will continue to incur losses for at least the next several years. We expect that our research and development and general and administrative expenses will continue to increase and, as a result, we will need additional capital to fund our operations, which we may raise through equity and/or debt financings. We may also consider new collaborations or selectively partnering our technology or programs.

Since inception through December 31, 2018, we have funded our operations primarily through the private placement of our convertible preferred stock from which we received net proceeds of $131.4 million, our initial public offering in April 2017, from which we received net proceeds of $86.9 million and our public offering in December 2018 from which we received net proceeds of $28.0 million. We have also received $44.0 million in net proceeds from term loans, $15.7 million in net proceeds from upfront and milestone payments under our license and collaboration agreements, $10.9 million from the issuance of our convertible promissory notes payable, and $2.6 million from private and federal grants.

In November 2018, we entered into the ATM facility with Citigroup, pursuant to which we may sell and issue shares of our common stock having an aggregate offering price of up to $30,000,000 from time to time through Citigroup, as our sales agent. As of December 31, 2018, we have not sold any shares of our common stock under the ATM facility.

The loans under our amended and restated loan and security agreement with two lenders, dated May 18, 2018, as amended, or the Loan Agreement, are secured by substantially all of our assets other than our intellectual property (except rights to payment from the sale, licensing of disposition of such intellectual property). As of December 31, 2018, there was $26.2 million outstanding under the Loan Agreement. Balances under the Loan Agreement accrue interest at the prime rate plus 3.75%, subject to a floor of 8.50%. The interest rate as of December 31, 2018 was 9.00%. The loans under the Loan Agreement mature in December 2022 with interest only payments through January 1, 2020 followed by 36 monthly payments of principal and interest, *provided* that the interest only period may be extended (and the number of principal and interest payments will be correspondingly reduced) in certain circumstances. The Loan Agreement contains customary conditions of borrowing, events of default and covenants, including covenants that restrict our ability to dispose of assets, merge with or acquire other entities, incur indebtedness and make distributions to holders of our capital stock. Should an event of default occur, including the occurrence of a material adverse change, we could be liable for immediate repayment of all obligations under the Loan Agreement.

As of December 31, 2018, we had $96.1 million in cash, cash equivalents and marketable securities. Our available cash and marketable securities are invested in accordance with our investment policy, primarily with a view to preserve principal and maintain liquidity.

Cash Flows

The following table sets forth the primary sources and uses of cash for each of the periods set forth below (in thousands):

	Years Ended December 31,		
	2018	2017	2016
Net cash provided by (used in):			
Operating activities	$ (34,469)	$ (31,133)	$ (29,539)
Investing activities	(4,190)	(27,707)	24,567
Financing activities	43,539	89,263	2,332
Net increase (decrease) in cash and cash equivalents	$ 4,880	$ 30,423	$ (2,640)

Operating Activities Net cash used in operating activities was $34.5 million for the year ended December 31, 2018, and consisted primarily of a net loss of $49.0 million adjusted for a net increase in cash from operating assets and liabilities of $6.1 million, noncash stock-based compensation expense of $6.9 million, depreciation expense of $0.6 million and noncash interest expense of $1.2 million. The $6.1 million net increase in cash from operating assets and liabilities is due primarily to a $5.4 million increase in our accounts payable and accrued liabilities resulting mainly from increases in clinical costs incurred to support our clinical trials and increase in our deferred rent of $1.0 million.

Net cash used in operating activities was $31.1 million for the year ended December 31, 2017, and consisted primarily of a net loss of $38.9 million adjusted for a net increase in cash from operating assets and liabilities of $2.5 million, noncash stock-based compensation expense of $4.5 million, depreciation expense of $0.3 million and noncash interest expense of $0.6 million. The $2.5 million net increase in cash from operating assets and liabilities is due primarily to a $3.3 million increase in our accounts payable and accrued liabilities resulting mainly from increases in clinical and manufacturing costs incurred to support our clinical trials and increased accrued payroll and related liabilities, primarily offset by a $0.7 million increase in prepaid expenses related to our clinical trial costs.

Net cash used in operating activities was $29.5 million for the year ended December 31, 2016, and consisted primarily of a net loss of $33.5 million adjusted for a net increase in cash from operating assets and liabilities of $1.9 million, noncash stock-based compensation expense of $1.3 million, depreciation expense of $0.3 million and noncash interest expense of $0.6 million. The $1.9 million net increase in cash from operating assets and liabilities is due primarily to a $2.1 million increase in our accounts payable and accrued liabilities resulting mainly from increases in clinical and manufacturing costs incurred to support our clinical trials and increased accrued payroll and related liabilities, primarily offset by a $0.2 million increase in prepaid expenses related to our clinical trial costs.

Investing Activities Net cash used in investing activities for the year ended December 31, 2018 was $4.2 million and consisted of purchases of marketable securities of $70.7 million and the purchase of property and equipment of $2.0 million offset primarily by proceeds from the maturity of marketable securities of $68.5 million.

Net cash used in investing activities for the year ended December 31, 2017 was $27.7 million and consisted of purchases of marketable securities of $70.8 million and purchases of property and equipment of $0.7 million, offset by sales and maturities of marketable securities of $43.7 million.

Net cash provided by investing activities for the year ended December 31, 2016 was $24.6 million and consisted primarily of proceeds received from the sale and maturities of marketable securities of $48.1 million, offset by purchases of marketable securities of $23.0 million and purchases of property and equipment of $0.5 million.

Financing activities Net cash provided by financing activities for the year ended December 31, 2018 was $43.5 million and consisted primarily of net proceeds from the issuance of notes payable of $26.3 million in May, upon refinancing our original debt agreement and net proceeds received from the sale of common stock of $28.0 million ($0.2 million of offering costs accrued as of December 31, 2018), offset by $11.6 million in principal and extinguishment payments on our original notes payable in conjunction with our May 2018 refinancing.

Net cash provided by financing activities for the year ended December 31, 2017 was $89.3 million and consisted primarily of net proceeds from our initial public offering of common stock of $88.6 million and $7.3 million from the issuance of convertible promissory notes payable and convertible promissory note subscriptions which were offset by $7.2 million in principal payments on our notes payable.

Net cash provided by financing activities for the year ended December 31, 2016 was $2.3 million and consisted of $3.5 million from the issuance of convertible promissory notes payable and convertible promissory note subscriptions which were partially offset by $0.6 million in principal payments on our notes payable and $0.6 million in cash paid for deferred equity issuance costs.

Funding Requirements

Our primary uses of capital are, and we expect will continue to be, compensation and related expenses for personnel, third-party clinical research and development services, laboratory expenses, regulatory expenses, marketing, and general and administrative expenses. Based on our research and development plans and our timing expectations related to the progress of our programs, we expect that our existing cash, cash equivalents and marketable securities as of December 31, 2018 will enable us to fund our operations for at least the next 12 months. We have based this estimate on assumptions that may prove to be wrong, and we could use our available capital resources sooner that we currently expect. Furthermore, our operating plan may change and we may need additional funds sooner than planned.

The successful development of any product candidate is highly uncertain. As such, at this time, we cannot reasonably estimate or know the nature, timing and costs of the efforts that will be necessary to complete the development of Toca 511 & Toca FC or our other current and future product candidates. We are also unable to predict when, if ever, material net cash inflows will commence from the sale of product candidates. This is due to the numerous risks and uncertainties associated with developing immunotherapies, including the uncertainty of:

- the progress, timing, costs and results of our ongoing Phase 3 clinical trial of Toca 511 & Toca FC;
- the progress, timing, costs and results of our Phase 1 dose escalation clinical trials that include our intratumoral study, resection study, and intravenous study;
- the progress, timing, costs and results of development for Toca 511 & Toca FC for the treatment of metastatic solid tumors;
- the progress, timing, costs and results of development for our other future product candidates;
- the outcome, timing and cost of regulatory approvals by the FDA and comparable foreign regulatory authorities, including the potential for the FDA or comparable foreign regulatory authorities to require that we perform more studies than those that we currently expect;
- the ability of our product candidates to progress through clinical development successfully;
- the cost of filing, prosecuting, defending and enforcing any patent claims and other intellectual property rights;
- arrangements with third-party service providers and manufacturers;
- our need and ability to hire additional personnel;
- our need to implement additional infrastructure and internal systems;
- the effect of competing technological and market developments; and
- the cost of establishing sales, marketing and distribution capabilities for any products for which we may receive regulatory approval.

A change in the outcome of any of these variables with respect to the development of any of our product candidates would significantly change the costs and timing associated with the development of that product candidate.

Until we can generate a sufficient amount of revenue from our products, if ever, we expect to finance future cash needs through equity and/or debt financings. We may also consider new collaborations or selectively partnering our technology or programs. Other than our ATM facility, we do not have any committed external source of funds. Additional capital may not be available on reasonable terms, if at all. Subject to limited exceptions, our Loan Agreement also prohibits us from incurring indebtedness without the prior written consent of the lenders. If we are unable to raise additional capital in sufficient amounts or on terms acceptable to us, we may have to significantly delay, scale back or discontinue the development or commercialization of one or more of our product candidates. If we raise additional funds through the issuance of additional equity or debt securities, it could result in dilution to our existing stockholders and increased fixed payment obligations, and these securities may have rights senior to those of our common stock. If we incur indebtedness, we could become subject to covenants that would restrict our operations and potentially impair our competitiveness, such as limitations on our ability to incur additional debt, limitations on our ability to acquire, sell or license intellectual property rights and other operating restrictions that could adversely impact our ability to conduct our business. Any of these events could significantly harm our business, financial condition and prospects.

Off-Balance Sheet Arrangements

We did not have during the periods presented, and we do not currently have, any off-balance sheet arrangements, as defined in the rules and regulations of the SEC.

Contractual Obligations and Commitments

The following table summarizes our contractual obligations and commitments as of December 31, 2018 that will affect our future liquidity (in thousands):

	Total	2019 <1 Year	2020-2021 2-3 Years	2022-2023 4-5 Years	> 5 Years
Notes payable	$ 28,553	$ —	$ 17,634	$ 10,919	$ —
Operating lease obligation	15,632	1,759	3,946	4,227	5,700
Total	$ 44,185	$ 1,759	$ 21,580	$ 15,146	$ 5,700

We also have obligations under license, collaboration and various grant agreements to make future payments to third parties that become due and payable on the achievement of certain commercial milestones. We have not included these commitments on our balance sheet or in the table above because the achievement and timing of these events is not fixed and determinable. These commitments are listed as follows:

- Pursuant to the technology license agreement with the University of Southern California, or USC, we are obligated to pay an annual royalty to USC starting in the second full calendar year when the net sales of products using the technology covered by the agreement reach a mid-seven-digit dollar range and until such time that the last valid claim of the patents covering our products expires. We are subject to pay interest if and when we become delinquent in our royalty payments.
- Pursuant to the collaborative agreement with Siemens, we are obligated to pay Siemens a royalty amount up to the mid-nine-digit dollar range per year on our brain cancer product sales in the first five years of such commercial sales.
- Pursuant to the agreement for a grant we received from Accelerate Brain Cancer Cure, Inc., or ABC2, we are obligated to pay an amount up to a maximum of $0.2 million to ABC2 if and when the net sales of our initial product candidate reach a total of $5.0 million within 10 years of the grant date. In addition, the ABC2 grant includes a conversion option whereby the payment amount may be converted, at our option, to common stock under certain circumstances.
- Pursuant to the agreement for a grant we received from the American Brain Tumor Association, or ABTA, we are obligated to pay an amount up to a maximum of $0.2 million to ABTA if and when the net sales of our initial product candidate reach a total of $5.0 million within 10 years of the ABTA grant date.
- Pursuant to the agreement for a grant we received from Voices Against Brain Cancer, or VABC, we are obligated to pay an amount up to a maximum of $0.3 million to VABC if and when we enter into a definitive agreement for a favorable transaction resulting in (a) the sale of all or substantially all of our capital stock in a transaction other than an initial public offering, (b) a favorable merger transaction of us with another entity, or (c) the sale of all or substantially all of our assets for cash within a certain time period. In addition, the VABC Grant includes a conversion option whereby VABC can elect to receive the payment in shares of our common stock under certain circumstances.

We enter into contracts in the ordinary course of business with clinical sites for the conduct of clinical trials, service providers for product manufacture and preclinical research studies, professional consultants for expert advice and other vendors for laboratory and research supplies and services. These contracts generally provide for termination on notice, and therefore are cancelable contracts and not included in the table of contractual obligations and commitments. In addition, these contracts have indemnification clause whereby we indemnify, defend, hold harmless and agree to reimburse the indemnified party for losses suffered or incurred by third party claims arising out of the indemnified party's performance of service. We have not incurred costs to defend lawsuits or settle claims related to these indemnification clauses.

Item 7A. Quantitative and Qualitative Disclosures About Market Risk.

The primary objective of our investment activities is to preserve our capital to fund our operations. We also seek to maximize income from our investments without assuming significant risk. To achieve our objectives, we maintain a portfolio of cash equivalents and investments in securities of high credit quality. As of December 31, 2018, we had cash, cash equivalents and marketable securities of $96.1 million consisting of cash and investments in certificates of deposit, money market funds, and investment-grade fixed income securities. A significant portion of our investments may be subject to interest rate risk and could fall in value if market interest rates increase. However, because our investments are primarily short-term in duration, we believe that our exposure to interest rate risk is not significant and a 1% movement in market interest rates would not have a significant impact on the total value of our portfolio. We actively monitor changes in interest rates.

We also have interest rate exposure as a result of our Loan Agreement. As of December 31, 2018, the outstanding principal amount under the Loan Agreement was $26.5 million. The term loan bears interest at a floating per annum rate equal to the greater of (i) 8.50% and (ii) the sum of (a) the prime rate reported in the Wall Street Journal on the last business day of the month that immediately proceeds the month in which the interest will accrue, plus (b) 3.75%. Changes in the U.S. Dollar prime rate may therefore affect our interest expense associated with the term loan.

If a 10% change in interest rates were to have occurred on December 31, 2018, this change would not have had a material effect on our interest expense as of that date.

Item 8. Financial Statements and Supplementary Data.

The financial statements and supplementary data required by this item are included after the Signatures page of this Annual Report on Form 10-K beginning on page F-1.

Item 9. Changes in and Disagreements With Accountants on Accounting and Financial Disclosure.

None.

Item 9A. Controls and Procedures.

Disclosure Controls and Procedures

We maintain disclosure controls and procedures that are designed to provide reasonable assurance that information required to be disclosed in our periodic and current reports that we file with the SEC is recorded, processed, summarized and reported within the time periods specified in the SEC's rules and forms, and that such information is accumulated and communicated to our management, including our principal executive officer and principal financial officer, as appropriate, to allow timely decisions regarding required disclosure. In designing and evaluating the disclosure controls and procedures, management recognizes that any controls and procedures, no matter how well designed and operated, can provide only reasonable and not absolute assurance of achieving the desired control objectives. In reaching a reasonable level of assurance, management is required to apply its judgment in evaluating the cost-benefit relationship of possible controls and procedures. In addition, the design of any system of controls also is based in part upon certain assumptions about the likelihood of future events, and there can be no assurance that any design will succeed in achieving its stated goals under all potential future conditions; over time, controls may become inadequate because of changes in conditions, or the degree of compliance with policies or procedures may deteriorate. Because of the inherent limitations in a cost-effective control system, misstatements due to error or fraud may occur and not be detected.

As of December 31, 2018, we carried out an evaluation under the supervision and with the participation of our management, including our principal executive officer and our principal financial officer, of the effectiveness of the design and operation of our disclosure controls and procedures, as defined in Rules 13a-15(e) and 15d-15(e) under the Securities Exchange Act of 1934, as amended, or Exchange Act. Based on this evaluation, our principal executive officer and principal financial officer concluded that our disclosure controls and procedures were effective at the reasonable assurance level as of December 31, 2018.

Management's Report on Internal Control over Financial Reporting

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

As of December 31, 2018, our management assessed the effectiveness of our internal control over financial reporting using the criteria set forth by the Committee of Sponsoring Organizations of the Treadway Commission in *Internal Control-Integrated Framework (2013 Framework).* Based on this assessment, our management concluded that, as of December 31, 2018, our internal control over financial reporting was effective based on those criteria.

Changes in Internal Control over Financial Reporting

There were no changes in our internal control over financial reporting that occurred during the most recent fiscal quarter ended December 31, 2018 that have materially affected, or are reasonably likely to materially affect, our internal control over financial reporting.

Item 9B. Other Information.

None.

PART III

Item 10. Directors, Executive Officers and Corporate Governance.

The information required by this item and not set forth below will be contained in our definitive proxy statement to be filed with the Securities and Exchange Commission in connection with our 2019 Annual Meeting of Stockholders, or the Proxy Statement, which is expected to be filed not later than 120 days after the end of our fiscal year ended December 31, 2018, and is incorporated herein by reference.

We have adopted a written Code of Business Conduct and Ethics, or Ethics Code, that applies to all officers, directors and employees, including our principal executive officer, principal financial officer, principal accounting officer or controller, or persons performing similar functions. The Ethics Code is available on our website at www.tocagen.com. If we make any substantive amendments to the Ethics Code or grant any waiver from a provision of the Ethics Code to any executive officer or director, we will promptly disclose the nature of the amendment or waiver on our website or in a current report on Form 8-K.

Item 11. Executive Compensation.

The information required by this item will be set forth in the Proxy Statement and is incorporated herein by reference.

Item 12. Security Ownership of Certain Beneficial Owners and Management and Related Stockholder Matters.

The information required by this item will be set forth in the Proxy Statement and is incorporated herein by reference.

Item 13. Certain Relationships and Related Transactions, and Director Independence.

The information required by this item will be set forth in the Proxy Statement and is incorporated herein by reference.

Item 14. Principal Accounting Fees and Services.

The information required by this item will be set forth in the Proxy Statement and is incorporated herein by reference.

PART IV

Item 15. Exhibits, Financial Statement Schedules.

(a)(1) Financial statements:

The Financial Statements of Tocagen Inc. and Report of Independent Registered Public Accounting Firm are included after the Signatures page of this Annual Report on Form 10-K beginning on page F-1.

(a)(2) Financial Statement Schedules:

These schedules have been omitted because the required information is included in the financial statements or notes thereto or because they are not applicable or not required.

(a)(3) Exhibits

Exhibit Index

Exhibit Number	Description
3.1	Amended and Restated Certificate of Incorporation of the Registrant, incorporated by reference to Exhibit 3.1 of the Registrant's Current Report on Form 8-K filed on April 19, 2017.
3.2	Amended and Restated Bylaws of the Registrant, incorporated by reference to Exhibit 3.2 of the Registrant's Current Report on Form 8-K filed on April 19, 2017.
4.1	Form of Common Stock Certificate of the Registrant, incorporated by reference to Exhibit 4.1 of the Registrant's Registration Statement on Form S-1 (File No. 333-216574), as amended, originally filed on March 9, 2017.
4.2	Warrant to Purchase Common Stock, dated June 5, 2013, issued to Voices Against Brain Cancer, incorporated by reference to Exhibit 4.2 of the Registrant's Registration Statement on Form S-1 (File No. 333-216574), as amended, originally filed on March 9, 2017.
4.3†	Research and Development Grant Agreement, dated June 5, 2013, by and between the Registrant and Voices Against Brain Cancer, incorporated by reference to Exhibit 4.3 of the Registrant's Registration Statement on Form S-1 (File No. 333-216574), as amended, originally filed on March 9, 2017.
4.4	Warrant to Purchase Stock, dated October 30, 2015, issued to Oxford Finance LLC, incorporated by reference to Exhibit 4.4 of the Registrant's Registration Statement on Form S-1 (File No. 333-216574), as amended, originally filed on March 9, 2017.
4.5	Warrant to Purchase Stock, dated October 30, 2015, issued to Silicon Valley Bank, incorporated by reference to Exhibit 4.5 of the Registrant's Registration Statement on Form S-1 (File No. 333-216574) , as amended, originally filed on March 9, 2017.
4.6	Warrant to Purchase Common Stock, dated May 18, 2018, issued to Oxford Finance LLC, incorporated by reference to Exhibit 4.6 of the Registrant's Quarterly Report on Form 10-Q filed on August 9, 2018.
4.7	Warrant to Purchase Common Stock, dated May 18, 2018, issued to Oxford Finance LLC, incorporated by reference to Exhibit 4.7 of the Registrant's Quarterly Report on Form 10-Q filed on August 9, 2018.
4.8	Warrant to Purchase Common Stock, dated May 18, 2018, issued to Oxford Finance LLC, incorporated by reference to Exhibit 4.8 of the Registrant's Quarterly Report on Form 10-Q filed on August 9, 2018.
4.9	Warrant to Purchase Common Stock, dated May 18, 2018, issued to Silicon Valley Bank, incorporated by reference to Exhibit 4.9 of the Registrant's Quarterly Report on Form 10-Q filed on August 9, 2018.
10.1+	Form of Indemnity Agreement by and between the Registrant and its directors and officers, incorporated by reference to Exhibit 10.1 of the Registrant's Registration Statement on Form S-1 (File No. 333-216574), as amended, originally filed on March 9, 2017.
10.2+	Tocagen Inc. 2009 Equity Incentive Plan and Forms of Option Grant Notice, Option Agreement and Notice of Exercise thereunder, as amended, incorporated by reference to Exhibit 10.2 of the Registrant's Registration Statement on Form S-1 (File No. 333-216574), as amended, originally filed on March 9, 2017.
10.3*	Tocagen Inc. 2017 Equity Incentive Plan, as amended, and Forms of Stock Option Grant Notice, Option Agreement and Notice of Exercise thereunder.
10.4+	Tocagen Inc. 2017 Employee Stock Purchase Plan, incorporated by reference to Exhibit 10.4 of the Registrant's Registration Statement on Form S-1 (File No. 333-216574), as amended, originally filed on March 9, 2017.
10.5†	Laboratory Services and License Agreement, effective as of November 17, 2011, by and between the Registrant and Siemens Healthcare Diagnostics Inc., incorporated by reference to Exhibit 10.7 of the Registrant's Registration Statement on Form S-1 (File No. 333-216574), as amended, originally filed on March 9, 2017.
10.6†	First Amendment to Laboratory Services and License Agreement, effective as of June 19, 2015, by and between the Registrant and Siemens Healthcare Diagnostics Inc., incorporated by reference to Exhibit 10.8 of the Registrant's Registration Statement on Form S-1 (File No. 333-216574), as amended, originally filed on March 9, 2017.
10.7†	License Agreement, effective as of October 22, 2007, by and between the Registrant and University of Southern California, incorporated by reference to Exhibit 10.9 of the Registrant's Registration Statement on Form S-1 (File No. 333-216574), as amended, originally filed on March 9, 2017.
10.8	Tocagen Inc. Annual Incentive Plan, incorporated by reference to Exhibit 10.1 of the Registrant's Quarterly Report on Form 10-Q filed on August 9, 2017.
10.9	Tocagen Inc. Amended and Restated Non-Employee Director Compensation Policy, incorporated by reference to Exhibit 10.11 of the Registrant's Annual Report on Form 10-K filed on March 9, 2018.
10.10+	Amended and Restated Executive Employment Agreement, dated February 12, 2018, by and between the Registrant and Martin J. Duvall, incorporated by reference to Exhibit 10.12 of the Registrant's Annual Report on Form 10-K filed on March 9, 2018.
10.11+	Amended and Restated Executive Employment Agreement, dated February 12, 2018, by and between the Registrant and Mark Foletta, incorporated by reference to Exhibit 10.13 of the Registrant's Annual Report on Form 10-K filed on March 9, 2018.

10.12+	Executive Employment Agreement, dated February 12, 2018, by and between the Registrant and Douglas Jolly, Ph.D., incorporated by reference to Exhibit 10.15 of the Registrant's Annual Report on Form 10-K filed on March 9, 2018.
10.13	Lease Agreement by and between the Registrant and AP3-SD1 Campus Point LLC, dated December 21, 2017, incorporated by reference to Exhibit 10.16 of the Registrant's Annual Report on Form 10-K filed on March 9, 2018.
10.14†	License Agreement, dated April 18, 2018, by and among the Registrant, Beijing Apollo Venus Biomedical Technology Limited and ApolloBio Corp., incorporated by reference to Exhibit 10.1 of the Registrant's Quarterly Report on Form 10-Q filed on August 9, 2018.
10.15	Amended and Restated Loan and Security Agreement, dated May 18, 2018, by and among the Registrant, Oxford Finance LLC and Silicon Valley Bank, incorporated by reference to Exhibit 10.2 of the Registrant's Quarterly Report on Form 10-Q filed on August 9, 2018.
10.16	First Amendment to Amended and Restated Loan and Security Agreement, dated August 3, 2018, by and amount the Registrant, Oxford Finance LLC and Silicon Valley Bank, incorporated by reference to Exhibit 10.3 of the Registrant's Quarterly Report on Form 10-Q filed on August 9, 2018.
23.1*	Consent of Independent Registered Public Accounting Firm.
24.1*	Power of Attorney (included on signature page).
31.1*	Certification of Principal Executive Officer Pursuant to Rules 13a-14(a) and 15d-14(a) under the Securities Exchange Act of 1934, as Adopted Pursuant to Section 302 of the Sarbanes-Oxley Act of 2002.
31.2*	Certification of Principal Financial Officer Pursuant to Rules 13a-14(a) and 15d-14(a) under the Securities Exchange Act of 1934, as Adopted Pursuant to Section 302 of the Sarbanes-Oxley Act of 2002.
32.1*	Certification of Principal Executive Officer and Principal Financial Officer Pursuant to 18 U.S.C. Section 1350, as Adopted Pursuant to Section 906 of the Sarbanes-Oxley Act of 2002.
101.INS*	XBRL Instance Document
101.SCH*	XBRL Taxonomy Extension Schema Document
101.CAL*	XBRL Taxonomy Extension Calculation Linkbase Document
101.DEF*	XBRL Taxonomy Extension Definition Linkbase Document
101.LAB*	XBRL Taxonomy Extension Label Linkbase Document
101.PRE*	XBRL Taxonomy Extension Label Linkbase Document

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* Filed herewith.

\+ Indicates management contract or compensatory plan.

† Confidential treatment has been granted with respect to certain portions of this exhibit. Omitted portions have been filed separately with the Securities and Exchange Commission.

Item 16. Form 10–K Summary.

None.

SIGNATURES

Pursuant to the requirements of Section 13 or 15(d) of the Securities Exchange Act of 1934, as amended, the registrant has duly caused this Annual Report on Form 10-K to be signed on its behalf by the undersigned, thereunto duly authorized**.**

TOCAGEN INC.

Date: February 27, 2019

By: /s/ MARTIN J. DUVALL
Martin J. Duvall
Chief Executive Officer
(Principal Executive Officer)

POWER OF ATTORNEY

KNOW ALL PERSONS BY THESE PRESENTS, that each person whose signature appears below constitutes and appoints Martin J. Duvall and Mark Foletta, and each of them, as his or her true and lawful attorneys-in-fact, each with full power of substitution, for him or her in any and all capacities, to sign any amendments to this Annual Report on Form 10-K and to file the same, with exhibits thereto and other documents in connection therewith, with the Securities and Exchange Commission, hereby ratifying and confirming all that each of said attorneys-in-fact or their substitute or substitutes may do or cause to be done by virtue hereof.

Pursuant to the requirements of the Securities Exchange Act of 1934, as amended, this report has been signed below by the following persons on behalf of the registrant in the capacities and on the dates indicated.

Signature	Title	Date
/s/ Martin J. Duvall **Martin J. Duvall**	Chief Executive Officer and Member of the Board of Directors *(Principal Executive Officer)*	February 27, 2019
/s/ Mark Foletta **Mark Foletta**	Chief Financial Officer *(Principal Financial and Accounting Officer)*	February 27, 2019
/s/ Faheem Hasnain **Faheem Hasnain**	Chairman of the Board of Directors	February 27, 2019
/s/ Franklin M. Berger **Franklin M. Berger**	Member of the Board of Directors	February 27, 2019
/s/ Thomas E. Darcy **Thomas E. Darcy**	Member of the Board of Directors	February 27, 2019
/s/ Harry E. Gruber, M.D. **Harry E. Gruber, M.D.**	Member of the Board of Directors	February 27, 2019
/s/ David Parkinson, M.D. **David Parkinson, M.D.**	Member of the Board of Directors	February 27, 2019
/s/ Paul Schimmel, Ph.D. **Paul Schimmel, Ph.D.**	Member of the Board of Directors	February 27, 2019

INDEX TO FINANCIAL STATEMENTS
TOCAGEN INC.

REPORT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

The Board of Directors and Stockholders of Tocagen Inc.

Opinion on the Financial Statements
We have audited the accompanying balance sheets of Tocagen Inc. (the Company) as of December 31, 2018 and 2017, and the related statements of operations and comprehensive loss, changes in convertible preferred stock and stockholders' equity (deficit) and cash flows for each of the three years in the period ended December 31, 2018, and the related notes (collectively referred to as the "financial statements"). In our opinion, the financial statements present fairly, in all material respects, the financial position of the Company at December 31, 2018 and 2017, and the results of its operations and its cash flows for each of the three years in the period ended December 31, 2018, in conformity with U.S. generally accepted accounting principles.

Basis for Opinion
These financial statements are the responsibility of the Company's management. Our responsibility is to express an opinion on the Company's financial statements based on our audits. We are a public accounting firm registered with the Public Company Accounting Oversight Board (United States) (PCAOB) and are required to be independent with respect to the Company in accordance with the U.S. federal securities laws and the applicable rules and regulations of the Securities and Exchange Commission and the PCAOB.

We conducted our audits in accordance with the standards of the PCAOB. Those standards require that we plan and perform the audit to obtain reasonable assurance about whether the financial statements are free of material misstatement, whether due to error or fraud. The Company is not required to have, nor were we engaged to perform, an audit of its internal control over financial reporting. As part of our audits we are required to obtain an understanding of internal control over financial reporting but not for the purpose of expressing an opinion on the effectiveness of the Company's internal control over financial reporting. Accordingly, we express no such opinion.

Our audits included performing procedures to assess the risks of material misstatement of the financial statements, whether due to error or fraud, and performing procedures that respond to those risks. Such procedures included examining, on a test basis, evidence regarding the amounts and disclosures in the financial statements. Our audits also included evaluating the accounting principles used and significant estimates made by management, as well as evaluating the overall presentation of the financial statements. We believe that our audits provide a reasonable basis for our opinion.

/s/ Ernst & Young LLP

We have served as the Company's auditor since 2008
San Diego, California
February 27, 2019

TOCAGEN INC.
BALANCE SHEETS
(in thousands, except share and par value data)

	December 31, 2018	December 31, 2017
ASSETS		
Current assets:		
Cash and cash equivalents	$ 40,813	$ 35,933
Marketable securities	55,273	52,792
Prepaid expenses and other current assets	1,662	1,904
Total current assets	97,748	90,629
Property and equipment, net	3,973	1,217
Other assets	1,360	227
Total assets	$ 103,081	$ 92,073
LIABILITIES AND STOCKHOLDERS' EQUITY		
Current liabilities:		
Accounts payable	$ 3,404	$ 1,951
Accrued liabilities	13,094	8,120
Notes payable, current portion	—	7,200
Deferred license revenue	36	36
Deferred grant funding	—	23
Total current liabilities	16,534	17,330
Notes payable, net of current portion	26,201	3,625
Deferred license revenue, net of current portion	—	36
Deferred rent, net of current portion	2,201	—
Total liabilities	44,936	20,991
Commitments and contingencies		
Stockholders' equity		
Common stock, $0.001 par value; 200,000,000 shares authorized at December 31, 2018 and 2017, respectively; 23,000,151 and 19,882,551 shares issued and outstanding at December 31, 2018 and December 31, 2017, respectively	23	20
Additional paid-in capital	274,029	238,025
Accumulated deficit	(215,884)	(166,929)
Accumulated other comprehensive loss	(23)	(34)
Total stockholders' equity	58,145	71,082
Total liabilities and stockholders' equity	$ 103,081	$ 92,073

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

TOCAGEN INC.
STATEMENTS OF OPERATIONS AND COMPREHENSIVE LOSS
(in thousands, except share and per share data)

	Years Ended December 31,		
	2018	**2017**	**2016**
License revenue	$ 18,036	$ 41	$ 49
Operating expenses:			
Research and development	51,080	29,113	27,218
General and administrative	12,809	8,556	4,521
Total operating expenses	63,889	37,669	31,739
Loss from operations	(45,853)	(37,628)	(31,690)
Other income (expense), net:			
Interest income	1,534	595	215
Interest expense	(2,937)	(1,932)	(2,052)
Change in fair value of preferred stock warrants	—	37	50
Loss before income taxes	(47,256)	(38,928)	(33,477)
Income tax expense	1,699	1	1
Net loss	$ (48,955)	$ (38,929)	$ (33,478)
Other comprehensive income (loss):			
Net unrealized gain (loss) on investments	11	(34)	58
Comprehensive loss	$ (48,944)	$ (38,963)	$ (33,420)
Net loss per common share, basic and diluted	$ (2.44)	$ (2.66)	$ (15.22)
Weighted-average number of common shares outstanding, basic and diluted	20,059,541	14,607,609	2,199,964

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

TOCAGEN INC.
STATEMENTS OF CHANGES IN CONVERTIBLE PREFERRED STOCK AND STOCKHOLDERS' EQUITY (DEFICIT)
(in thousands, except share and per share data)

	Convertible Preferred Stock		Common Stock		Additional Paid-In Capital	Accumulated Deficit	Accumulated Other Comprehensive Income (Loss)	Total Stockholders' Equity (Deficit)
	Shares	Amount	Shares	Amount				
Balance at December 31, 2015	46,163,605	131,413	2,197,852	2	2,238	(94,512)	(58)	(92,330)
Cumulative effect of accounting change	—	—	—	—	10	(10)	—	—
Balance at January 1, 2016	46,163,605	131,413	2,197,852	2	2,248	(94,522)	(58)	(92,330)
Exercise of stock options	—	—	4,665	—	10	—	—	10
Stock-based compensation	—	—	—	—	1,323	—	—	1,323
Other comprehensive income	—	—	—	—	—	—	58	58
Net Loss	—	—	—	—	—	(33,478)	—	(33,478)
Balance at December 31, 2016	46,163,605	131,413	2,202,517	2	3,581	(128,000)	—	(124,417)
Exercise of stock options	—	—	55,669	—	81	—	—	81
Issuance of common stock pursuant to employee stock purchase plan	—	—	50,121	—	426	—	—	426
Stock-based compensation	—	—	—	—	4,451	—	—	4,451
Fractional shares adjustment upon reverse stock split	—	—	2	—	—	—	—	—
Preferred stock converted into shares of common stock	(46,163,605)	(131,413)	6,690,066	7	131,403	—	—	131,410
Initial public offering of common shares, net of issuance costs	—	—	9,775,000	10	86,938	—	—	86,948
Convertible promissory notes converted into shares of common stock, net of issuance costs	—	—	1,109,176	1	11,056	—	—	11,057
Preferred stock warrant liabilities converted into warrants to purchase shares of common stock	—	—	—	—	89	—	—	89
Other comprehensive loss	—	—	—	—	—	—	(34)	(34)
Net Loss	—	—	—	—	—	(38,929)	—	(38,929)
Balance at December 31, 2017	—	—	19,882,551	20	238,025	(166,929)	(34)	71,082
Exercise of stock options	—	—	45,073	—	67	—	—	67
Issuance of common stock pursuant to employee stock purchase plan	—	—	72,527	—	594	—	—	594
Issuance of common stock, net of offering costs	—	—	3,000,000	3	27,994	—	—	27,997
Stock-based compensation	—	—	—	—	6,870	—	—	6,870
Issuance of common stock warrants	—	—	—	—	479	—	—	479
Other comprehensive loss	—	—	—	—	—	—	11	11
Net Loss	—	—	—	—	—	(48,955)	—	(48,955)
Balance at December 31, 2018	—	$ —	23,000,151	$ 23	$ 274,029	$ (215,884)	$ (23)	$ 58,145

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

TOCAGEN INC.
STATEMENTS OF CASH FLOWS
(in thousands)

	Years Ended December 31,		
	2018	2017	2016
OPERATING ACTIVITIES			
Net loss	$ (48,955)	$ (38,929)	$ (33,478)
Adjustments to reconcile net loss to net cash used in operating activities:			
Stock-based compensation	6,870	4,451	1,323
Depreciation	625	292	255
Noncash interest expense	1,161	590	570
Change in fair value of preferred stock warrants	—	(37)	(50)
Accretion of discount on investments, net	(248)	(19)	(9)
Gain on disposal of property and equipment	—	—	(20)
Changes in operating assets and liabilities:			
Prepaid expenses and other current assets	(208)	(679)	(157)
Accounts payable	1,260	304	586
Accrued liabilities	4,127	2,946	1,547
Deferred license revenue	(36)	(41)	(49)
Deferred rent	958	—	—
Deferred grant funding	(23)	(11)	(57)
Net cash used in operating activities	(34,469)	(31,133)	(29,539)
INVESTING ACTIVITIES			
Proceeds from the sale/maturity of marketable securities	68,524	43,725	48,095
Purchases of marketable securities	(70,746)	(70,797)	(23,003)
Purchases of property and equipment	(1,968)	(655)	(525)
Proceeds from sale of property and equipment	—	20	—
Net cash (used in) provided by investing activities	(4,190)	(27,707)	24,567
FINANCING ACTIVITIES			
Proceeds from issuance of notes payable, net of issuance costs	26,325	—	—
Cash paid on extinguishment of debt	(8,631)	—	—
Principal payments on notes payable	(3,000)	(7,200)	(600)
Proceeds from issuance of common stock	661	507	10
Proceeds from public offering of common stock, net of issuance costs	28,200	88,618	—
Proceeds from issuance of convertible promissory notes, net of issuance costs	—	7,338	3,374
Proceeds from convertible promissory note subscriptions	—	—	140
Cash paid for deferred equity issuance costs	(16)	—	(592)
Net cash provided by financing activities	43,539	89,263	2,332
Net increase (decrease) in cash and cash equivalents	4,880	30,423	(2,640)
Cash and cash equivalents, beginning of period	35,933	5,510	8,150
Cash and cash equivalents, end of period	$ 40,813	$ 35,933	$ 5,510
SUPPLEMENTAL DISCLOSURES OF CASH FLOW INFORMATION			
Cash paid for interest	$ 1,522	$ 1,210	$ 1,460
Allowance for tenant improvements included in deferred rent	$ 1,243	$ —	$ —
Property and equipment purchases included in accounts payable and accrued liabilities	$ 178	$ 111	$ 28
Fair value of common stock warrants issued in connection with notes payable	$ 479	$ —	$ —
Convertible preferred stock converted into shares of common stock	$ —	$ 131,410	$ —
Convertible promissory notes principal and accrued interest converted into shares of common stock	$ —	$ 11,057	$ —
Preferred stock warrant liabilities converted into warrants to purchase shares of common stock	$ —	$ 89	$ —
Deferred equity issuance costs paid in previous periods reclassified to equity on effective date of initial public offering	$ —	$ 1,574	$ —
Deferred equity issuance costs in accounts payable and accrued liabilities	$ 310	$ 96	$ 226

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

1. Organization and Basis of Presentation

Tocagen Inc. (Tocagen or the Company) is a clinical-stage, cancer-selective gene therapy company focused on developing first-in-class, broadly-applicable product candidates designed to activate a patient's immune system against their own cancer. The Company's cancer-selective gene therapy platform is built on retroviral replicating vectors which are designed to selectively deliver therapeutic genes into the DNA of cancer cells. Tocagen's gene therapy approach is designed to fight cancer through immunotherapeutic mechanisms of action without the autoimmune toxicities commonly experienced with other immunotherapies. The Company views its operations and manages its business in one operating segment.

From inception through December 31, 2018, the Company has devoted substantially all of its efforts to developing its gene therapy platform and its lead product candidate, Toca 511 & Toca FC, as well as raising capital and building its infrastructure. The Company has not generated revenues from its principal operations.

Initial Public Offering

On April 19, 2017, the Company completed its initial public offering (IPO), whereby the Company sold an aggregate of 9,775,000 shares of its common stock, at $10.00 per share, resulting in net proceeds of $86.9 million after underwriting discounts, commissions and offering costs of $10.8 million.

In addition, in connection with the IPO, all of the Company's outstanding shares of convertible preferred stock were converted into an aggregate of 6,690,066 shares of the Company's common stock, warrants to purchase up to 68,572 shares of the Company's Series H convertible preferred stock were converted into warrants to purchase up to 9,936 shares of the Company's common stock, each at an exercise price of $36.23 per share, and $11.1 million of aggregate principal and accrued interest underlying convertible promissory notes were automatically converted into an aggregate of 1,109,176 shares of the Company's common stock at the IPO price of $10.00 per share.

ATM Facility

In November 2018, the Company entered into an Equity Distribution Agreement with Citigroup Global Markets Inc. ("Citigroup"), pursuant to which the Company may sell and issue shares of its common stock having an aggregate offering price of up to $30,000,000 from time to time through Citigroup, as its sales agent (the "ATM facility"). As of December 31, 2018, the Company has not sold any shares of its common stock under the ATM facility.

Public Offering

In December 2018, the Company completed a public offering in which it sold an aggregate of 3,000,000 shares of common stock at a price of $10.00 per share. Net proceeds from the public offering, after deducting underwriting discounts, commissions and offering expenses, were approximately $28.0 million.

Liquidity

The Company has a limited operating history and the sales and income potential of the Company's business and patient markets are unproven. The Company has experienced net losses and negative cash flows from operating activities since its inception. As of December 31, 2018, the Company had an accumulated deficit of $215.9 million and working capital of $81.2 million available to fund future operations. As the Company continues to incur net losses, its transition to profitability is dependent upon the successful development, approval, and commercialization of its product candidates and achieving a level of revenues adequate to support the Company's cost structure. The Company may never achieve profitability, and unless and until it does, the Company will continue to need to raise additional capital. The Company plans to continue to fund its losses from operations and capital funding needs through debt and equity financing, or through collaborations or partnerships with other entities. Debt or equity financing, or collaborations and partnerships with other entities may not be available on a timely basis on terms acceptable to the Company, or at all.

As of December 31, 2018, the Company had cash, cash equivalents and marketable securities of $96.1 million. The Company has evaluated and concluded that there are no conditions or events, considered individually or in the aggregate, that raises substantial doubt about its ability to continue as a going concern for a period of one year following the date that these financial statements are issued.

Use of Estimates

The Company's financial statements are prepared in accordance with accounting principles generally accepted in the United States, which requires management to make estimates and assumptions that affect the reported amounts of assets, liabilities, revenue and expenses and the disclosure of contingent assets and liabilities in the financial statements accompanying notes. Significant estimates in the Company's financial statements relate to clinical trial accruals, the valuation of equity awards, and the development period used for license revenue recognition. Estimates are periodically reviewed in light of changes in circumstances, facts and experience. Actual results may differ from these estimates under different assumptions or conditions.

2. Summary of Significant Accounting Policies

Cash, Cash Equivalents and Marketable Securities

Cash consists of the balance in a readily available checking account. Cash equivalents consist of money market funds, corporate debt securities and certificates of deposit with remaining maturities of three months or less at the time of purchase, and are considered highly liquid investments. Marketable securities consist of corporate debt securities, commercial paper, U.S. treasury securities and asset-backed securities that have original maturities greater than three months at the time of purchase.

The Company classifies its investments as available-for-sale and records such assets at fair value in the balance sheet, with unrealized gains and losses, if any, reported in stockholders' equity. Realized gains and losses are calculated on the specific identification method and recorded to interest income.

A decline in the market value of any marketable security below cost that is determined to be other-than-temporary results in a revaluation of its carrying amount to fair value and a new cost basis for the security. Impairment losses are recognized in other expense in the statement of operations.

Concentration of Credit Risk and Off-Balance Sheet Risk

Financial instruments that potentially subject the Company to significant concentration of credit risk consist primarily of cash equivalents and marketable securities. The Company's investment policy includes guidelines for the quality of the related institutions and financial instruments, and defines allowable investments that the Company may invest in, which the Company believes minimizes the exposure to concentration of credit risk.

Prepaid Expenses and Other Current Assets

Prepaid expenses and other current assets primarily represent amounts related to insurance, clinical trial and manufacturing agreements, and investment interest receivable.

Property and Equipment

Property and equipment is stated at cost and depreciated over the estimated useful lives of the assets (three to five years) using the straight-line method. Leasehold improvements are depreciated using the straight-line method over the lesser of the remaining lease term or an estimated useful life of five years.

Costs of major additions and betterments are capitalized and depreciated on a straight-line basis over their useful lives. Repairs and maintenance costs are expensed as incurred. Upon retirement or sale, the cost of assets disposed of and the related accumulated depreciation are removed from the accounts, and any resulting gain or loss is credited or charged to expense.

Deferred Equity Issuance Costs

Specific incremental costs directly attributable to an offering of securities are deferred and charged against the gross proceeds of the offering through additional paid-in capital.

Impairment of Long-Lived Assets

Long-lived assets consist of property and equipment. An impairment loss is recorded if and when events and circumstances indicate that assets might be impaired and the undiscounted cash flows estimated to be generated by those assets are less than the carrying amount of those assets. No impairment loss has been recognized for the years ended December 31, 2018 and 2017.

Fair Value of Financial Instruments

The Company's financial instruments consist principally of cash, cash equivalents, marketable securities, prepaid expenses, other current assets, accounts payable and notes payable. The carrying amounts of these financial instruments approximate the related fair values due to the short-term maturities of these instruments.

The authoritative accounting guidance defines fair value, establishes a consistent framework for measuring fair value and expands disclosure for each major asset and liability category measured at fair value on either a recurring or nonrecurring basis. Fair value is defined as an exit price, representing the amount that would be received to sell an asset or paid to transfer a liability in an orderly transaction between market participants. As such, fair value is a market-based measurement that should be determined based on assumptions that market participants would use in pricing an asset or liability. As a basis for considering such assumptions, the authoritative accounting guidance establishes a three-tier fair value hierarchy that prioritizes the inputs used in measuring fair value as follows:

Level 1: Observable inputs such as quoted prices in active markets;

Level 2: Inputs, other than the quoted prices in active markets, that are observable either directly or indirectly such as quoted prices for similar assets or liabilities, quoted prices in markets that are not active, or other inputs that are observable or can be corroborated by observable market data for substantially the full term of the assets or liabilities; and

Level 3: Unobservable inputs that are supported by little or no market activity and that are significant to the fair value of the assets or liabilities.

Clinical Trial Accruals

Expenses related to clinical studies are based on estimates of the services received and efforts expended pursuant to the Company's contract arrangements. The financial terms of these agreements are subject to negotiation, vary from contract to contract and may result in uneven payment flows. There may be instances in which payments made to the Company's service providers will temporarily exceed the level of services provided and result in a prepayment of the clinical expense. Payments under some of these contracts depend on factors such as the successful enrollment of patients, site initiation and the completion of clinical milestones. The Company makes estimates of its accrued expenses as of each balance sheet date in its financial statements based on facts and circumstances known at that time. In accruing service fees, the Company estimates the time period over which services will be performed and the level of effort to be expended in each period. If the actual timing of the performance of services or the level of effort varies from its estimate, the Company adjusts the accrual or prepaid expense balance accordingly. Historically, the Company's estimated accrued liabilities have materially approximated actual expense incurred.

Revenue Recognition

On January 1, 2018, the Company adopted Accounting Standards Update (ASU) 2014-09, *Revenue from Contract with Customers (Topic 606)*, using the modified retrospective transition method. There was no impact to opening retained earnings or revenue as of January 1, 2018 related to the adoption of Topic 606. Revenue generally consists of license revenue with upfront payments and development milestones considered probable of achievement.

Revenue is recognized when control of the promised goods or services is transferred to the Company's customers in an amount that reflects the consideration the Company expects to receive from its customers in exchange for those goods and services. This process involves identifying the contract with a customer, determining the performance obligations in the contract, determining the transaction price, allocating the contract price to the distinct performance obligations in the contract, and recognizing revenue when or as the Company satisfies the performance obligation(s).

At contract inception, the Company assesses the goods and services promised within each contract and assesses whether each promised good or service is distinct and determines that those are performance obligations. A performance obligation is considered distinct from other obligations in a contract when it provides a benefit to the customer either on its own or together with other resources that are readily available to the customer and is separately identified in the contract. The Company considers factors such as the research, manufacturing and commercialization capabilities of the collaboration partner and the availability of the associated expertise in the general marketplace. The Company considers a performance obligation satisfied once the Company has transferred control of a good or service to the customer, meaning the customer has the ability to use and obtain the benefit of the good or service. The Company recognizes revenue for satisfied performance obligations only when the Company determines there are no uncertainties regarding payment terms or transfer of control.

Collaborative Arrangements

The Company enters into collaborative arrangements with partners that may include payment to the Company of one or more of the following: (i) license fees; (ii) payments related to the achievement of developmental, regulatory, or commercial milestones; and (iii) royalties on net sales of licensed products. Where a portion of non-refundable upfront fees or other payments received are allocated to continuing performance obligations under the terms of a collaborative arrangement, they are recorded as contract liabilities and recognized as revenue when (or as) the underlying performance obligation is satisfied.

As part of the accounting for these arrangements, the Company must develop estimates and assumptions that require judgment to determine the underlying stand-alone selling price for each performance obligation which determines how the transaction price is allocated among the performance obligation(s). The stand-alone selling price may include items such as forecasted revenues, development timelines, discount rates, and probabilities of technical and regulatory success. The Company evaluates each performance obligation to determine if it can be satisfied at a point in time or over time. In addition, variable consideration must be evaluated to determine if it is constrained and, therefore, excluded from the transaction price.

License Fees

If a license to the Company's intellectual property is determined to be distinct from the other performance obligations identified in the arrangement, the Company recognizes revenues from non-refundable, upfront fees allocated to the license when the license is transferred to the licensee and the licensee is able to use and benefit from the license. For licenses that are bundled with other promises, the Company utilizes judgment to assess the nature of the combined performance obligation to determine whether the combined performance obligation is satisfied over time or at a point in time and, if over time, the appropriate method of measuring progress for purposes of recognizing revenue. The Company evaluates the measure of progress each reporting period and, if necessary, adjusts the measure of performance and related revenue recognition. Any such adjustments are recorded on a cumulative catch-up basis, which would affect license, collaboration or other revenues and earnings in the period of adjustment.

Milestone Payments

At the inception of each arrangement that includes milestone payments (variable consideration), the Company evaluates whether the milestones are considered probable of being reached and estimates the amount to be included in the transaction price. If it is probable that a milestone event would occur at the inception of the arrangement, the associated milestone value is included in the transaction price. Milestone payments that are not within the Company's control, such as regulatory approvals, are generally not considered probable of being achieved until those approvals are received. The transaction price is then allocated to each performance obligation on a relative stand-alone selling price basis, for which the Company recognizes revenue as or when the performance obligations under the contract are satisfied. At the end of each reporting period, the Company evaluates the probability of achievement of such milestones and any related constraint(s), and if necessary, may adjust the Company's estimate of the overall transaction price. Any such adjustments are recorded on a cumulative catch-up basis, which would affect license, collaboration or other revenues and earnings in the period of adjustment.

Royalties

For arrangements that include sales-based royalties, including milestone payments based on the level of sales, and for which the license is deemed to be the predominant item to which the royalties relate, the Company recognizes revenue at the later of (i) when the related sales occur, or (ii) when the performance obligation to which some or all of the royalty has been allocated has been satisfied (or partially satisfied). To date, the Company has not recognized any royalty revenue resulting from its collaborative arrangements.

Research and Development Costs

Research and development expenses consist primarily of salaries and other personnel related expenses including non-cash stock-based compensation costs, preclinical costs, clinical trial costs, costs related to acquiring and manufacturing clinical trial materials, contract services, facilities costs, overhead costs, and depreciation. All research and development costs are expensed as incurred.

Patent Costs

Costs related to filing and pursuing patent applications are recorded as general and administrative expense and expensed as incurred because recoverability of such expenditures is uncertain.

Grant Funding

The Company receives certain research and development funding through grants from nonprofit organizations that serve the brain cancer community. The Company evaluates the terms of each grant to assess the Company's obligations, and such funding is recognized in the statement of operations as a reduction to research and development expense as the related costs are incurred to meet those obligations over the grant period. Certain grants contain repayment provisions contingent on future events, such as future revenue milestones related to the Company's lead product candidate under development. For each repayment provision, the Company assesses if it is obligated to repay the funds provided by the other parties regardless of the outcome of the funded research and development. For each arrangement, the Company also reviews the repayment provisions to determine the likelihood of repayment at the execution of each grant and on an ongoing basis. If the likelihood of repayment of a grant is determined to be remote and the Company is not obligated to repay the funds regardless of the outcome of the funded research and development, the grant is recognized as a reduction to research and development expense as related costs are incurred over the grant period. The Company subsequently reviews the repayment provisions of each grant at each reporting date and will record a related grant repayment liability if and when such repayment obligation is determined to be probable. If, at the execution of a grant with repayment provisions, the probability of repayment is probable, the Company will record the grant as a liability until such time as the grant requirements have been satisfied and the repayment provisions have lapsed.

Debt Issuance Costs

Debt issuance costs incurred to obtain debt financing are deferred and are amortized over the term of the debt using the effective interest method. The costs are recorded as a reduction to the carrying value of the debt and the amortization expense is included in interest expense in the statement of operations.

Warrants for Shares of Common Stock

The Company accounts for warrants for shares of common stock as equity instruments in the accompanying balance sheets at their fair value on the date of issuance because such warrants are indexed to the Company's common stock and no cash settlement is required except for (i) liquidation of the Company, or (ii) a change in control in which the common stockholders also receive cash.

Income Taxes

The Company accounts for income taxes under the asset and liability method, which requires the recognition of deferred tax assets and liabilities for the expected future tax consequences that have been included in the financial statements. Under this method, deferred tax assets and liabilities are determined on the basis of the differences between the financial statements and tax basis of assets and liabilities using enacted tax rates in effect for the year in which the differences are expected to reverse. The Company provides a valuation allowance against net deferred tax assets unless, based upon the available evidence, it is more likely than not that the deferred tax assets will be realized.

The Company records uncertain tax positions on the basis of a two-step process whereby (i) management determines whether it is more likely than not that the tax positions will be sustained on the basis of the technical merits of the position and (ii) for those tax positions that meet the more likely-than-not recognition threshold, management recognizes the largest amount of tax benefit that is more than 50 percent likely to be realized upon ultimate settlement with the related tax authority. The Company will recognize interest and penalties in income tax expense if and when incurred.

Comprehensive Income (Loss)

All components of comprehensive income (loss) are reported in the financial statements in the period in which they are recognized. Other comprehensive income (loss) is defined as the change in equity during a period from transactions and other events and circumstances from non-owner sources, including unrealized gains and losses on investments. The Company's only component of other comprehensive loss is unrealized gains (losses) on investments. Comprehensive gains (losses) have been reflected in the statements of operations and comprehensive loss for all periods presented.

Stock-Based Compensation

Stock-based compensation expense represents the cost of the grant date fair value of stock awards, including stock options, and stock purchase rights granted to employees and members of the Company's board of directors. For awards with time-based vesting provisions, the Company estimates the fair value of stock options on the date of grant using the Black-Scholes option pricing model and recognizes the expense over the requisite service period of the awards, which is generally the vesting period, on a straight-line basis. For awards with performance-based vesting provisions, the Company estimates the fair value of stock option grants on the date of grant, or the date when all of the terms of the grant have been agreed to, if later, and recognizes the expense based on the probability of the occurrence of the individual milestones at each reporting period. The expense is recognized over the implicit service period that commences once management believes the performance criteria are probable of being met. For purchase rights, the Company estimates the fair value of the purchase as of the plan enrollment date and recognizes expense on a straight-line basis over the applicable offering period. The Company accounts for forfeitures when they occur, and reverses any compensation cost previously recognized for awards for which the requisite service has not been completed, in the period that the award is forfeited.

Net Loss Per Share

Basic and diluted net loss per common share for the periods presented is computed by dividing net loss by the weighted-average number of common shares outstanding during the respective periods, without consideration of common stock equivalents as they are anti-dilutive. Common stock equivalents that could potentially dilute earnings in the future are comprised of shares issuable upon the conversion of all outstanding principal and accrued interest related to convertible promissory notes payable, shares issuable upon the conversion of convertible preferred stock, options to purchase shares of common stock outstanding under the Company's equity incentive plan and warrants for the purchase of shares of common and preferred stock. For all periods presented, there is no difference in the number of shares used to calculate basic and diluted shares outstanding due to the Company's net loss position.

Common stock equivalents from potentially dilutive securities, excluding shares issuable upon the conversion of all outstanding principal and accrued interest related to convertible promissory notes, that are not included in the calculation of diluted net loss per share, because to do so would be anti-dilutive, are as follows:

	Years Ended December 31,		
	2018	2017	2016
Common stock options	3,476,847	2,589,348	1,385,855
Common stock warrants	67,238	10,660	724
Convertible preferred stock (as-converted)	—	—	6,690,066
Convertible preferred stock warrants (as-converted)	—	—	9,936
Total	3,544,085	2,600,008	8,086,581

Recent Accounting Pronouncements

In February 2016, the FASB issued ASU 2016-02, *Leases (Topic 842)*, which requires lessees to recognize most leases on their balance sheet as lease liabilities with corresponding right-of-use assets and disclose key information about leasing arrangements. The new standard is effective for the Company beginning in the first quarter of 2019 and requires a modified retrospective approach for all leases existing at, or entered into after, the date of initial application, with an option to elect to use certain transition relief. The Company has completed its identification of leases which is comprised of one building lease. The Company is in the process of quantifying the impact to the balance sheet while the impact to the statement of operations is expected to be immaterial.

In June 2018, the FASB issued ASU 2018-07, *Compensation- Stock Compensation (Topic 718), Improvements to Nonemployee Share-Based Payment Accounting*. This new standard is intended to simplify aspects of share-based compensation issued to non-employees by aligning the accounting for share-based payment awards issued to employees and non-employees as it relates to the measurement date and impact of performance conditions. The new standard will become effective January 1, 2019 and does not have a material impact to the overall financial statements of the Company.

3. Fair Value of Financial Instruments

Fair Values of Assets Measured on a Recurring Basis

The following tables summarize the Company's assets that require fair value measurements on a recurring basis and their respective input levels based on the fair value hierarchy (in thousands):

		Fair Value Measurements at End of Period Using:		
	Total	Quoted Market Prices for Identical Assets (Level 1)	Significant Other Observable Inputs (Level 2)	Significant Unobservable Inputs (Level 3)
December 31, 2018				
Cash equivalents:				
Corporate debt securities	$ 4,783	$ —	$ 4,783	$ —
Commercial paper	1,987	—	1,987	—
	$ 6,770	$ —	$ 6,770	$ —
Marketable securities:				
Corporate debt securities	$ 16,301	$ —	$ 16,301	$ —
Commercial paper	24,576	—	24,576	—
U.S. treasury securities	1,997	1,997	—	—
Asset-backed securities	12,399	—	12,399	—
	$ 55,273	$ 1,997	$ 53,276	$ —

		Fair Value Measurements at End of Period Using:		
	Total	Quoted Market Prices for Identical Assets (Level 1)	Significant Other Observable Inputs (Level 2)	Significant Unobservable Inputs (Level 3)
December 31, 2017				
Cash equivalents:				
Corporate debt securities	$ 8,274	$ —	$ 8,274	$ —
Repurchase agreements	5,000	—	5,000	—
	$ 13,274	$ —	$ 13,274	$ —
Marketable securities:				
Corporate debt securities	$ 24,713	$ —	$ 24,713	$ —
Certificates of deposit	13,651	—	13,651	—
Commercial paper	12,329	—	12,329	—
Asset-backed securities	2,099	—	2,099	—
	$ 52,792	$ —	$ 52,792	$ —

Marketable Securities. For fair values determined by Level 1 inputs, which utilize quoted prices in active markets for identical assets, the level of judgment required to estimate fair value is relatively low. The fair values of investments in U.S. treasury securities were determined using Level 1 inputs.

Fair values determined by Level 2 inputs, which utilize data points that are observable such as quoted prices, interest rates and yield curves, require the exercise of judgment and use of estimates, that if changed, could significantly affect the Company's financial position and results of operations. Investments in corporate debt securities, certificates of deposit, commercial paper, repurchase agreements and asset-backed securities are valued using Level 2 inputs. Level 2 securities are initially valued at the transaction price and subsequently valued and reported utilizing inputs other than quoted prices that are observable either directly or indirectly, such as quotes from third-party pricing vendors.

There were no transfers in or out of Level 1 or Level 2 investments during the years ended December 31, 2018 or 2017.

At December 31, 2018 and 2017, the Company had investments in money market funds of $30.9 million and $20.2 million, respectively, that were measured at fair value using the net asset value per share (or its equivalent) that have not been classified in the fair value hierarchy. The funds invest primarily in U.S. government securities.

Warrant Liabilities. The Company had preferred stock warrants that were treated as liabilities and measured at fair value on a recurring basis. All preferred stock warrants outstanding converted into warrants to purchase shares of common stock in the connection with the Company's IPO. The Company recorded a gain on warrant valuation, which was included in other expense, of $37,000 for the year ended December 31, 2017. Upon conversion of the preferred stock warrants, the Company recorded $0.1 million to additional paid in capital and reduced the preferred stock warrant liability to zero.

Fair Values of Other Financial Instruments

The carrying amounts of certain of the Company's financial instruments, including cash and accounts payable, approximate their respective fair values due to their short-term nature. The carrying amount of the Company's notes payable of $26.2 million at December 31, 2018 approximated their fair value as the terms of the notes are consistent with the market terms of transactions with similar profiles (Level 2 inputs).

4. Certain Financial Statement Caption Information

Marketable Securities

The following is a summary of the Company's marketable securities (in thousands):

	Maturity (in years)	Amortized Cost	Unrealized Gain	Unrealized Loss	Fair Value
December 31, 2018					
Corporate debt securities	1 or less	$ 10,013	$ 1	$ (4)	$ 10,010
Corporate debt securities	>1 and <5	6,293	2	(4)	6,291
Commercial paper	1 or less	24,584	—	(8)	24,576
U.S. treasury securities	1 or less	1,997	—	—	1,997
Asset-backed securities	1 or less	10,612	—	(8)	10,604
Asset-backed securities	>1 and <5	1,797		(2)	1,795
		$ 55,296	$ 3	$ (26)	$ 55,273
December 31, 2017					
Corporate debt securities	1 or less	$ 21,097	$ —	$ (16)	$ 21,081
Corporate debt securities	>1 and <5	3,636	—	(4)	3,632
Certificates of deposit	1 or less	13,658	—	(7)	13,651
Commercial paper	1 or less	12,333	—	(4)	12,329
Asset-backed securities	1 or less	2,099	—	—	2,099
		$ 52,823	$ —	$ (31)	$ 52,792

The Company has classified all of its available-for-sale investment securities, including those with maturity greater than one year, as current assets on the balance sheet based on the highly liquid nature of these investment securities and because these investment securities are considered available for use in current operations.

There were no impairments considered other-than-temporary during the periods presented, as it is management's intention and ability to hold the securities until a recovery of the cost basis or recovery of fair value. Gross realized gains and losses on sales of marketable securities were immaterial for all periods presented.

Property and Equipment

Property and equipment is comprised of (in thousands):

	December 31,	
	2018	2017
Laboratory equipment	$ 4,445	$ 3,553
Computers, software and office equipment	322	232
Furniture and fixtures	610	21
Leasehold improvements	1,927	117
	7,304	3,923
Less: accumulated depreciation	(3,331)	(2,706)
	$ 3,973	$ 1,217

Depreciation expense was $0.6 million and $0.3 million for the years ended December 31, 2018 and 2017, respectively.

Accrued Liabilities

Accrued liabilities are comprised of (in thousands):

	December 31,	
	2018	2017
Clinical trial expenses	$ 4,535	$ 2,809
Payroll and other employee-related expenses	2,840	2,489
Contract manufacturing services	3,411	1,536
Professional fees	474	276
Interest payable	205	77
Other	1,629	933
Total accrued liabilities	$ 13,094	$ 8,120

5. Notes Payable

Loan Agreement

On October 30, 2015, the Company entered into a Loan and Security Agreement (Prior Agreement) with two lenders whereby it borrowed $18.0 million (the Initial Loans). Balances under the Prior Agreement were due in monthly principal and interest payments, with final maturity of the Initial Loans in May 2019. Each Initial Loan included a final payment fee of 7.95% of the original principal amount due upon maturity.

On May 18, 2018, the Company entered into an Amended and Restated Loan and Security Agreement with the two lenders, which was further amended on August 3, 2018 (the Loan Agreement), pursuant to which the lenders agreed to lend the Company $26.5 million as term loans (the Term Loans). Of the total proceeds, $8.6 million was applied to the repayment of outstanding principal, interest and final payment owed pursuant to the Initial Loans.

The Company evaluated the May 2018 Amended and Restated Loan and Security Agreement in accordance with ASC Topic 470, which requires assessment of whether the modification is considered a substantial modification, in which case the modification would be accounted for as a debt extinguishment. Based on the Company's evaluation, the May 2018 Amended and Restated Loan and Security Agreement was considered substantial and therefore the unamortized discount associated with the Prior Agreement was written off through interest expense and the principal balance of the Prior Agreement was written off.

The Term Loans will mature on December 1, 2022 (the Maturity Date) and the Company will have interest-only payments through January 1, 2020, followed by 36 equal monthly payments of principal and interest; *provided* that the Term Loans will be interest-only (and the number of principal and interest payments will be correspondingly reduced) through (i) July 1, 2020 if the Company submits a Biologics License Application (BLA) for the Company's product candidate, Toca 511 & Toca FC, to the United States Food and Drug Administration (FDA) prior to January 1, 2020, but not yet received FDA approval of such BLA prior to July 1, 2020 and (ii) January 1, 2021 if following such BLA submission to the FDA prior to January 1, 2020, the Company receives FDA approval of such BLA prior to July 1, 2020.

The Term Loans bear interest at a floating per annum rate equal to the greater of (i) 8.50% and (ii) the sum of (a) the prime rate reported in the Wall Street Journal on the last business day of the month that immediately proceeds the month in which the interest will accrue, plus (b) 3.75%. The Company will be required to make a final payment of 7.95% of the principal amount of the Term Loans payable on the earlier of (i) the Maturity Date, (ii) the acceleration of any Term Loans, or (iii) the prepayment of the Term Loans. The Company may prepay all, but not less than all, of the Term Loans upon 10 days written notice provided the Company will be obligated to pay a prepayment fee equal to (i) 3.00% of the principal amount of the applicable Term Loan prepaid on or before the first anniversary of the effective date of the Loan Agreement, (ii) 2.00% of the principal amount of the applicable Term Loan prepaid on or before the second anniversary of the effective date of the Loan Agreement, and (iii) 1.00% of the principal amount of the applicable Term Loan prepaid thereafter, but prior to the Maturity Date.

In conjunction with the Loan Agreement, the Company issued the lenders warrants exercisable for 56,578 shares of common stock (the Warrants). The Warrants are exercisable in whole or in part, immediately, and have a per share exercise price of $9.35. The Warrants will terminate on the earlier of May 18, 2028 or the closing of a certain merger or consolidation transaction. The Company recorded the Warrants as a debt discount, which is a contra-liability against debt, and is amortizing the balance over the life of the

underlying debt. The offset to the contra-liability is recorded as additional paid in capital in the Company's balance sheet as the Warrants were determined to be an equity instrument. The Company determined the fair value of the Warrants at the date of issuance was $0.5 million using the Black-Scholes option pricing model based on significant unobservable inputs (Level 3) with an expected term of 10 years, volatility of 85.6%, risk free rate of 3.1% and expected dividend of 0%.

The costs incurred to issue the Term Loans of $0.1 million were deferred and are included in the discount to the carrying value of the Term Loans in the accompanying balance sheet. The deferred costs and the final payment fee are amortized to interest expense over the expected term of the Term Loans using the effective interest method with an effective interest rate of 10.7%.

The aggregate carrying amounts of the Term Loans and Initial Loans are comprised of the following, as applicable (in thousands):

	December 31,	
	2018	2017
Principal	$ 26,450	$ 10,200
Add: accreted liability for final payment fee	276	869
Less: unamortized discount	(525)	(244)
	$ 26,201	$ 10,825

The Term Loans are secured by substantially all of the Company's assets other than its intellectual property, except rights to payment from the sale, licensing or disposition of such intellectual property. The Company is also required to maintain its primary operating accounts at all times with one of the lenders. The Loan Agreement contains customary conditions of borrowing, events of default and covenants, including covenants that restrict the Company's ability to dispose of assets, merge with or acquire other entities, incur indebtedness and make distributions to holders of its capital stock. Should an event of default occur, including the occurrence of a material adverse change, the Company could be liable for immediate repayment of all obligations under the Loan Agreement. As of December 31, 2018, the Company was in compliance with the covenants contained in the Loan Agreement.

Future maturities of the Term Loans, including the final payment fee, as of December 31, 2018 are as follows (in thousands):

	December 31, 2018
Year ending December 31, 2019	$ —
Year ending December 31, 2020	8,817
Year ending December 31, 2021	8,817
Year ending December 31, 2022	10,919
	28,553
Unaccreted balance for final payment fee on Loans	(1,827)
Unamortized discounts	(525)
Noncurrent portion	$ 26,201

Convertible Promissory Notes

Upon completion of the Company's IPO in April 2017, $11.1 million of aggregate principal and accrued interest underlying convertible promissory notes were automatically converted into an aggregate of 1,109,176 shares of the Company's common stock at the IPO price of $10.00 per share.

6. Stockholders' Equity

Upon completion of the Company's IPO, all of the Company's outstanding shares of convertible preferred stock were converted into an aggregate of 6,690,066 shares of the Company's common stock. As of December 31, 2018, the Company's authorized capital stock consists of 200,000,000 shares of common stock, par value $0.001 per share, and 10,000,000 shares of preferred stock, par value $0.001 per share.

In December 2018, the Company completed a public offering in which it sold an aggregate of 3,000,000 shares of common stock at a price of $10.00 per share. Net proceeds from the public offering, after deducting underwriting discounts, commissions and offering expenses, were approximately $28.0 million.

Common Stock Reserved for Future Issuance

Common stock reserved for future issuance as of December 31, 2018 and 2017 is as follows:

	December 31,	
	2018	2017
Issued and Outstanding:		
Stock options	3,476,847	2,589,348
Warrants for common stock	67,238	10,660
Shares reserved for issuance under the ESPP	326,178	199,879
Shares reserved for future award grants	451,063	513,333

7. Equity Incentive Plans and Stock-Based Compensation

2017 Equity Incentive Plan

In March 2017, the Company's board of directors and stockholders approved and adopted the Company's 2017 Equity Incentive Plan, which became effective on April 12, 2017 and was subsequently amended September 30, 2018 (the 2017 Plan). The 2017 Plan provides for the grant of incentive stock options (ISOs), nonstatutory stock options, stock appreciation rights, restricted stock awards, restricted stock unit awards, performance-based stock awards, other forms of equity compensation and performance cash awards. ISOs may be granted only to employees. All other awards may be granted to employees, including officers, and to non-employee directors and consultants of the Company and its affiliates.

Initially, 1,600,000 new shares of common stock were approved for issuance under the 2017 Plan and, on April 12, 2017, 75,517 shares of common stock reserved for issuance under the Company's 2009 Equity Incentive Plan, as amended (the 2009 Plan), were added to the shares initially reserved under the 2017 Plan. No further grants will be made under the 2009 Plan and any shares subject to outstanding stock options under the 2009 Plan that would otherwise be returned to the 2009 Plan will instead be added to the shares reserved under the 2017 Plan. Additionally, the number of shares of common stock reserved for issuance under the 2017 Plan will automatically increase on January 1 of each calendar year through January 1, 2027, by 4% of the total number of shares of the Company's capital stock outstanding on December 31 of the preceding calendar year, or a lesser number of shares determined by the Company's board of directors.

All grants of options to purchase common stock under the 2017 Plan expire in 10 years. Grants with time-based vesting provisions are subject to a four-year vesting schedule with 25% vesting after the first year, and the balance vesting monthly over the remaining 36 months. Grants with performance-based vesting provisions vest upon the achievement of three separate development and regulatory milestones, with one-third of the options vesting upon the achievement of each milestone.

The following table summarizes stock option activity under the Company's equity incentive plans for the year ended December 31, 2018:

	Shares Subject to Options	Weighted-Average Exercise Price per Share	Weighted-Average Remaining Contractual Term (in years)	Aggregate Intrinsic Value (in thousands)
Options Outstanding at December 31, 2017	2,589,348	$ 13.33		
Granted	1,222,150	$ 11.08		
Exercised	(45,073)	$ 1.49		
Forfeitures and cancellations	(289,578)	$ 13.60		
Options Outstanding at December 31, 2018	3,476,847	$ 12.67	7.7	$ 1,481
Options Exercisable at December 31, 2018	1,358,986	$ 11.77	6.1	$ 1,481

The following table summarizes certain information regarding stock options (in thousands):

	Years Ended December 31,		
	2018	2017	2016
Fair value of options vested during the period	$ 6,318	$ 2,194	$ 1,087
Cash received from options exercised during the period	$ 67	$ 81	$ 10
Intrinsic value of options exercised during the period	$ 508	$ 677	$ 62

The aggregate intrinsic value of options is calculated as the difference between the exercise price of the options and the fair value of the Company's common stock for those options that had exercise prices lower than the fair value of the Company's common stock.

2017 Employee Stock Purchase Plan

In March 2017, the Company's board of directors and stockholders approved and adopted the Company's 2017 Employee Stock Purchase Plan (ESPP) whereby eligible employees may elect to withhold up to 15% of their earnings to purchase shares of the Company's common stock at a price per share equal to the lower of (i) 85% of the fair market value of a share of the Company's common stock on the first date of an offering or (ii) 85% of the fair market value of a share of the Company's common stock on the date of purchase (purchase right). The ESPP became effective on April 12, 2017. Initially, 250,000 shares of the Company's common stock were approved for issuance under the ESPP pursuant to purchase rights granted to the Company's employees or to employees of any of the Company's designated affiliates. The number of shares of common stock reserved for issuance will automatically increase on January 1 of each calendar year through January 1, 2027, by the lesser of (a) 1% of the total number of shares of the Company's common stock outstanding on December 31 of the preceding calendar year, (b) 300,000 shares, or (c) a number determined by the Company's board of directors that is less than (a) and (b).

As of December 31, 2018, the Company had issued 122,648 shares of common stock under the ESPP, with 72,527 of such shares of common stock being issued during the year ended December 31, 2018. The Company had 326,178 shares available for future issuance under the ESPP as of December 31, 2018.

Stock-Based Compensation Expense

The weighted average assumptions used in the Black-Scholes option pricing model to determine the fair value of the employee stock option grants with both time-based and performance-based vesting provisions and stock purchase rights were as follows:

	Years Ended December 31,		
	2018	2017	2016
Time based stock options			
Risk-free interest rate	2.7%	2.0%	1.63%
Volatility	85.9%	82.2%	73.4%
Dividend yield	0%	0%	0%
Expected term (in years)	6.1	6.1	6.1
Grant date fair value per share	$ 8.12	$ 10.39	$ 9.69
Performance based stock options			
Risk-free interest rate	—	2.1%	—
Volatility	—	75.9%	—
Dividend yield	—	0%	—
Expected term (in years)	—	6.3	—
Grant date fair value per share	$ —	$ 6.73	$ —
Employee stock purchase plan			
Risk-free interest rate	2.5%	1.2%	—
Volatility	78.1%	69.8%	—
Dividend yield	0%	0%	—
Expected term (in years)	1.1	1.3	—
Grant date fair value per share	$ 5.02	$ 4.61	$ —

Risk-free interest rate. The Company bases the risk-free interest rate assumption on U.S. Treasury constant maturities with maturities similar to those of the expected term of the award being valued.

Expected volatility. Due to the Company's limited trading of its common stock and lack of company-specific historical or implied volatility data, the Company has based its estimate of expected volatility on the historical volatility of a group of similar companies in the life sciences industry whose shares are publicly traded. The Company selects the peer group based on comparable characteristics, including development stage, product pipeline, and enterprise value. The Company computes historical volatility data using the daily closing prices for the selected companies' shares during the equivalent period of the calculated expected term of the stock-based awards. The Company will continue to apply this process until sufficient amount of historical information regarding the volatility of its own stock price become available.

Expected term. The expected term of employee stock options granted with time-based vesting provisions was calculated using the simplified method which utilizes the midpoint between the weighted average time of vesting and the end of the contractual term. The expected term of employee stock options granted with performance-based vesting provisions was calculated using the midpoint between the estimated service period and the contractual term of the option. These methods were utilized due to a lack of historical exercise behavior by the Company's employees. The expected term for stock purchase rights is the term from the date of grant to the date of purchase.

Expected dividend yield. The Company bases the expected dividend yield assumption on the fact that it has never paid, and does not expect to pay, dividends in the foreseeable future.

The Company has not recognized non-cash stock-based compensation expense for outstanding options to purchase 188,651 shares of common stock with performance-based vesting provisions after its evaluation that the occurrence of the individual milestones is not probable as of December 31, 2018.

Total non-cash stock-based compensation expense for all stock awards and purchase rights, net of forfeitures recognized as they occur, that was recognized in the statements of operations is as follows (in thousands):

	Years Ended December 31,		
	2018	2017	2016
Research and development	$ 3,023	$ 1,783	$ 562
General and administrative	3,847	2,668	761
Total	$ 6,870	$ 4,451	$ 1,323

Unrecognized compensation expense for stock options at December 31, 2018 was $17.1 million which is expected to be recognized over a weighted-average period of 2.5 years.

8. License and Collaboration Agreements

ApolloBio License

On April 18, 2018, the Company entered into a License Agreement (the License Agreement) with Beijing Apollo Venus Biomedical Technology Limited and ApolloBio Corp. (collectively, ApolloBio), which became effective in July 2018, pursuant to which the Company granted to ApolloBio an exclusive license to develop and commercialize Toca 511 & Toca FC within the greater China region, including mainland China, Hong Kong, Macao and Taiwan (the Licensed Territory).

Under the License Agreement, the Company has received net proceeds of $15.2 million which is comprised of a $16.0 million up-front payment and a $2.0 million development milestone payment less $1.7 million in foreign income taxes and $1.1 million in certain foreign non-income taxes. The foreign income taxes were recorded as income tax expense and the foreign non-income taxes were recorded as a general and administrative expense, on the statement of operations during the year ended December 31, 2018.

The Company is eligible to receive up to an aggregate $111.0 million, less withholding and other taxes, upon the achievement of specified development and commercial milestones. The Company completed its planned enrollment of 380 patients in the Toca 5 clinical trial in 2018 and earned a $2.0 million development milestone payment. The Company is also eligible for low double-digit tiered royalty payments based on annual net sales of licensed products in the Licensed Territory, subject to reduction under specified circumstances. ApolloBio will be responsible for all development and commercialization costs in the Licensed Territory. Future payments by ApolloBio are subject to the People’s Republic of China (PRC) currency exchange approval and may be subject to other approvals by PRC authorities.

Unless earlier terminated, the License Agreement will expire upon the expiration of the last-to-expire royalty term for any and all licensed products, which royalty term is, with respect to a licensed product in a particular region (*i.e.*, mainland China, Hong Kong, Macao and Taiwan) of the Licensed Territory (each, a Region), the latest of (i) 10 years after the first commercial sale of such licensed product in such Region, (ii) the expiration of all regulatory exclusivity as to such licensed product in such Region and (iii) the date of expiration of the last valid patent claim covering such licensed product in such Region. Either party may terminate the License Agreement upon a material breach by the other party that remains uncured following 60 days (or, with respect to any payment breach, 10 days) after the date of written notice of such breach. ApolloBio may terminate the License Agreement at any time by providing 90 days’ prior written notice to the Company. In addition, the Company may terminate the License Agreement upon written notice to ApolloBio under specified circumstances if ApolloBio challenges the licensed patent rights.

Under Topic 606, the Company evaluated the terms of the License Agreement and the transfer of intellectual property rights (the "license") was identified as the only performance obligation as of the inception of the License Agreement. The Company determined that the transaction price under the License Agreement was comprised solely of the $16.0 million upfront payment. The future potential development and commercial milestone payments were not included in the transaction price as they were determined to be fully constrained. As part of the evaluation of the development and commercial milestone constraint, the Company determined that the achievement of such milestones is contingent upon success in future clinical trials and regulatory approvals, each of which was uncertain at the inception of the License Agreement. The Company will re-evaluate the transaction price each quarter or as uncertain events are resolved or other changes in circumstances occur. Future potential development and commercial milestone amounts would be recognized as revenue, if unconstrained. Any reimbursable program costs are recognized proportionately with the performance of the underlying services and are accounted for as a reduction to research and development expense and are excluded from the transaction price.

The entire $16.0 million transaction price was allocated to the license performance obligation. The license was delivered in connection with the execution of the License Agreement and the performance obligation was fully satisfied (transfer of intellectual property). Additionally, the Company earned a $2.0 million development milestone payment upon completion of the planned enrollment of 380 patients in the Toca 5 clinical trial. The Company has recorded total revenue of $18.0 million for the year ended December 31, 2018 related to the License Agreement.

9. Grant Agreements

In August 2017, the Company was awarded a $2.0 million grant by the U.S. Food and Drug Administration Office of Orphan Products Development to support its Phase 3 clinical trial (OOPD Grant). Under the grant agreement, the Company will be reimbursed for qualifying expenses over a four-year period subject to the availability of funds and satisfactory progress of the trial. The Company received reimbursable amounts of $0.5 million for each of the years ended December 31, 2018 and 2017 relating to the OOPD Grant as an offset against research and development costs incurred during the period.

10. Income Taxes

Significant components of the income tax expense are as follows (in thousands):

	Year ended December 31,		
	2018	2017	2016
Current			
Federal	$ —	$ —	$ —
State	1	1	1
Foreign	1,698	—	—
Total current provision	1,699	1	1
Deferred			
Federal	—	—	—
State	—	—	—
Total Deferred	—	—	—
Income Tax Expense	$ 1,699	$ 1	$ 1

The (benefit) provision for income taxes differs from the amount of income tax determined by applying the applicable U.S. statutory federal income tax rate to pretax income as a result of the following differences:

	Years Ended December 31,		
	2018	2017	2016
Federal statutory rate	21.0%	34.0%	34.0%
Adjustments for tax effects of:			
State taxes, net	6.1%	5.7%	5.6%
Withholding Tax	(3.6)%	—%	—%
Permanent adjustments	(1.0)%	(4.5)%	(5.4)%
Tax Cuts and Jobs Act	—%	(3.7)%	—%
Net operating loss carryovers not recognized	(22.1)%	(30.4)%	(32.8)%
Valuation allowance	(5.9)%	(1.0)%	(1.1)%
Other	1.9%	(0.1)%	(0.3)%
Effective income tax rate	(3.7)%	—%	—%

Deferred taxes are recognized for temporary differences between the basis of assets and liabilities for financial statement and income tax purposes. Significant components of the Company's deferred taxes are as follows (in thousands):

	December 31,	
	2018	2017
Deferred tax assets:		
Depreciation and amortization	$ —	$ 52
Deferred license revenue	10	15
Share-based compensation	3,432	1,459
Debt discount	137	—
Accrued liabilities and other	1,778	808
Total deferred tax assets	5,357	2,334
Less valuation allowance	(5,107)	(2,334)
Net deferred tax assets	$ 250	$ —
Deferred tax liabilities:		
Depreciation and amortization	$ (250)	$ —
Total Deferred tax liabilities	$ (250)	$ —
Net deferred taxes	$ —	$ —

The Company has evaluated the positive and negative evidence bearing upon the realizability of its deferred tax assets. Based upon the Company's history of operating losses, the Company has concluded that it is more likely than not that the benefit of its deferred tax assets will not be realized. Accordingly, the Company has provided a full valuation allowance for deferred tax assets as of December 31, 2018 and 2017. During 2018 and 2017, the valuation allowance increased by $2.6 million and $0.4 million, respectively.

The Company has federal and California net operating loss carryforwards which may be available to offset future income tax liabilities. As of December 31, 2018, the Company has federal net operating losses of $174.1 million, of which, $136.6 million begin expiring in 2028 unless previously utilized and $37.6 million that do not expire but are limited to 80% of taxable income in a given year. The Company has California net operating loss carryforwards of $76.1 million that begin to expire in 2028 unless previously utilized as of December 31, 2018. Excluded from the California net operating loss carryforward are net operating losses for the years ended December 31, 2013, 2014, 2015, 2016 and 2017 which were impacted by a California Supreme Court ruling on December 31, 2015. This ruling clarified how companies are allowed to apportion income or losses in the state. As a result of the ruling, the Company has completed an analysis to determine the re-apportionment of its losses to California using the required single sales factor market sourcing method for 2013 through 2017 by treating its passive interest income as California-source income which results in a 100% apportionment percentage to California. While this portion may not reach the more-likely-than-not recognition threshold, the Company has excluded a cumulative net operating loss of $109.3 million from its California net operating loss carryforward.

As of December 31, 2018, the Company has federal and California research and development tax credit carryforwards of $25.6 million and $6.1 million, respectively. The federal research and development tax credits begin to expire in 2028 unless previously utilized. The California credits do not expire.

Pursuant to Internal Revenue Code (IRC) Sections 382 and 383, annual use of a company's net operating loss and tax credit carryforwards may be limited if there is a cumulative change in ownership of greater than 50% within a three-year period. The amount of the annual limitation is determined based on the value of the Company immediately prior to the ownership change. Subsequent ownership changes may further affect the limitation in future years. The Company has completed several equity offerings since its inception which may have resulted in a change in control as defined by Sections 382 and 383 of the IRC, or could result in a change in control in the future. The Company has not completed an IRC Section 382 and 383 analysis regarding the limitation of net operating loss and research and development credit carryforwards. Until such an analysis has been completed, the Company has removed the deferred tax assets for net operating losses of $42.0 million and federal and California research and development credits of approximately $30.4 million from its deferred tax asset schedule, and has recorded a corresponding decrease to its valuation allowance. When this analysis is finalized, the Company plans to update its unrecognized tax benefits accordingly. The Company does not expect this analysis to be completed within the next 12 months and, as a result, the Company does not expect that the unrecognized tax benefits will change within 12 months of this reporting date. Due to the existence of the valuation allowance, future changes in the Company's unrecognized tax benefits will not impact the Company's effective tax rate.

The Company's policy is to record interest and penalties relating to uncertain tax positions as a component of income tax expense. As of December 31, 2018 and 2017, there was no accrued interest or penalties for uncertain tax positions.

The Company is subject to taxation in the U.S. and state jurisdictions. As of December 31, 2018, the Company's tax years beginning 2007 to date are subject to examination by federal and California taxing authorities due to the carry forward of unutilized net operating losses and research and development tax credits. To the extent the Company has tax attribute carryforwards, the tax years in which the attribute was generated may still be adjusted upon examination by the Internal Revenue Service or state tax authorities to the extent utilized in a future period.

Pursuant to the federal tax legislation that was enacted on December 22, 2017 (the Tax Act), the Company re-measured its existing deferred tax assets and liabilities based on 21%, the current rate at which they are expected to reverse in the future. In 2017, the Company recorded provisional amounts for certain enactment-date effects of the Act by applying the guidance in SAB 118 because it had not yet completed the enactment-date accounting for these effects. In 2018 and 2017, the Company did not record tax expense related to the enactment-date effects of the Act as the Company maintained a full valuation allowance. Upon completion of the Company's analysis of certain aspects of the Act and refinement of the calculations during the year ended December 31, 2018, the Company found no other adjustments were necessary.

11. Retirement Plan

The Company sponsors an employee savings plan that qualifies as a deferred salary arrangement under Section 401(k) of the IRC. Participating employees may defer up to the Internal Revenue Service annual contribution limit. The Company has elected to match 50% of an employee's contributions up to 6% of the employees' eligible salary beginning January 1, 2019. The Company has not made any contributions for the years ended December 31, 2018, 2017 and 2016.

12. Commitments and Contingencies

Leases and Other Commitments

The Company leases its office and laboratory space located in San Diego, California, under an operating lease agreement (the Lease). The Lease commenced in March 2018. The term of the Lease is eight years and the Company has one option to extend the Lease for a period of five additional years.

In connection with the inception of the Lease, the Company was provided and fully utilized a tenant improvement allowance of $1.2 million. As of December 31, 2018 the Company has used the full allowance, which is classified as tenant improvements and deferred rent on the Company's balance sheet and will be amortized against rent expense on a straight line basis over the term of the Lease. The Lease provides for an abatement of a portion of the lease payments for the first nine months of the lease term and includes escalation clauses in the future.

Future annual minimum rental payments payable under the Lease are as follows (shown in thousands):

Years ended December 31:	
2019	$ 1,759
2020	1,939
2021	2,007
2022	2,077
2023	2,150
Thereafter	5,700
Total	$ 15,632

The Company enters into service agreements with indemnification clauses in the ordinary course of business. Pursuant to such clauses, the Company indemnifies, defends, holds harmless, and agrees to reimburse the indemnified party for losses suffered or incurred by third party claims arising out of the indemnified party's performance of service. The Company has not incurred costs to defend lawsuits pursuant to these indemnification clauses.

Legal Proceedings

From time to time, the Company may be involved in various claims and legal proceedings relating to claims arising out of the Company's operations. The Company is not currently a party to any legal proceedings that, in the opinion of management, are likely to have a material adverse effect on the Company's business. Regardless of outcome, litigation can have an adverse impact on the Company because of defense and settlement costs, diversion of management resources and other factors.

13. Selected Quarterly Financial Data (unaudited)

The following table contains unaudited quarterly financial information for the years ended December 31, 2018 and 2017. The Company believes that the following information reflects all normal recurring adjustments necessary for a fair statement of the information for the periods presented. The operating results for any quarter are not necessarily indicative of results for any future period.

	First Quarter	Second Quarter	Third Quarter	Fourth Quarter
Year Ended December 31, 2018				
Operating expenses	$ 12,855	$ 15,336	$ 16,582	$ 19,116
Net loss	(12,880)	(16,089)	(383)	(19,603)
Net loss per common share, basic and diluted	$ (0.65)	$ (0.81)	$ (0.02)	(0.96)
Year Ended December 31, 2017				
Operating expenses	$ 8,564	$ 8,662	$ 9,747	$ 10,696
Net loss	(9,073)	(9,066)	(9,953)	(10,837)
Net loss per common share, basic and diluted	$ (4.11)	$ (0.56)	$ (0.50)	$ (0.55)

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CORPORATE INFORMATION

EXECUTIVE OFFICERS

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Chief Executive Officer

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President, Science and Innovation

Mark G. Foletta
Executive Vice President and Chief Financial Officer

Lori Kunkel, MD
Acting Chief Medical Officer

Douglas J. Jolly, PhD
Executive Vice President, Research and Pharmaceutical Development

John F. Wood
Senior Vice President, Regulatory Affairs and Quality Assurance

Nicholas A. Boyle, PhD
Vice President, Corporate Strategy and Business Development

Carlos E. Ibañez, PhD
Vice President, Product Development and Manufacturing

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Vice President, Biometrics

Sophie Visonneau, PhD
Vice President, Clinical Operations

Mohamed H. Ladha
Vice President, Head of Commercial and Medical Affairs

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Founder and Managing Director of FMB Research

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Co-Founder of Tocagen and Board Member

Faheem Hasnain
Co-Founder and Executive Chairman, Gossamer Bio

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Chief Executive Officer, Tocagen

David R. Parkinson, MD
President and Chief Executive Officer, ESSA Pharma

Paul Schimmel, PhD
Hahn Professor of Molecular Biology and Chemistry at The Scripps Research Institute

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ANNUAL MEETING

May 29, 2019 | 10:00 a.m. PDT
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Tocagen™

No One Should Die Of Cancer™

Tocagen is a clinical-stage, cancer-selective gene therapy company developing first-in-class, broadly applicable product candidates designed to activate a patient's immune system against their own cancer. Tocagen's lead investigational product candidate, Toca 511 & Toca FC, is under evaluation in a pivotal Phase 3 trial for recurrent high grade glioma (HGG), a disease with significant unmet medical need. The U.S. Food and Drug Administration awarded Tocagen an orphan drug grant for the Toca 5 trial and has granted Toca 511 & Toca FC Breakthrough Therapy Designation for the treatment of recurrent HGG. The European Medicines Agency has granted Toca 511 PRIME (PRIority MEdicines) designation for the treatment of glioma.