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UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
WASHINGTON, DC 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

☐ **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: 001-36054

Sophiris Bio Inc.
(Exact name of registrant as specified in its charter)

British Columbia **(State or Other Jurisdiction of Incorporation or Organization)**	**98-1008712** **(I.R.S. Employer Identification No.)**
1258 Prospect Street, La Jolla, California **(Address of Principal Executive Offices)**	**92037** **(Zip Code)**

858-777-1760
(Registrant's Telephone Number, Including Area Code)

Indicate by check mark if the registrant is a well-known season 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 Securities Exchange Act of 1934. 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 ☐

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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 filer pursuant to Item 405 of Regulation S-K (§229.405 of this chapter) is not contained herein, and will not be contained, to the best of the 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 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 registrant is a shell company (as defined in Rule 12b-2 of the Exchange Act). ☐ Yes ☒ No

As of June 29, 2018, the last business day of the registrant's most recently completed second fiscal quarter, the aggregate market value of the registrant's common shares held by non-affiliates of the registrant was approximately $84.5 million, based on the closing price of the registrant's common shares on The Nasdaq Capital Market on June 29, 2018 of $2.81.

As of March 4, 2019, the registrant had 30,217,140 common shares (no par value) outstanding.

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the registrant's definitive Proxy Statement for the 2019 Annual Meeting of Shareholders to be filed with the Securities and Exchange Commission by April 30, 2019 are incorporated by reference into Part III of this report.

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PART I.

FORWARD-LOOKING STATEMENTS

This Annual Report on Form 10-K and the information incorporated herein by reference contain forward-looking statements that involve a number of risks and uncertainties. Although our forward-looking statements reflect the good faith judgment of our management, these statements can only be based on facts and factors currently known by us. Consequently, these forward-looking statements are inherently subject to risks and uncertainties, and actual results and outcomes may differ materially from results and outcomes discussed in the forward-looking statements.

Forward-looking statements include statements about our strategies, objectives, discoveries, clinical trials, development programs, financial forecasts and other statements that are not historical facts, including statements which may be preceded by the words "intend," "will," "plan," "expect," "anticipate," "estimate," "aim," "seek," "suggest," "may," "believe," "hope" or similar words. Similarly, statements that describe our future plans, strategies, intentions, expectations, objectives, goals or prospects and other statements that are not historical facts are also forward-looking statements. These statements include but are not limited to statements under the captions "Business," "Risk Factors," and "Management's Discussion and Analysis of Financial Condition and Results of Operations" as well as other sections in this Annual Report on Form 10-K. You should be aware that the occurrence of any of the events discussed under the heading "Item 1A. Risk Factors" and elsewhere in this report could substantially harm our business, results of operations and financial condition and that if any of these events occurs, the trading price of our common shares could decline and you could lose all or a part of the value of your common shares. The cautionary statements made in this report are intended to be applicable to all related forward-looking statements wherever they may appear in this Annual Report on Form 10-K. We urge you not to place undue reliance on these forward-looking statements, which speak only as of the date of this Annual Report on Form 10-K. Except as required by law, we assume no obligation to update our forward-looking statements, even if new information becomes available in the future.

All dollar amounts are expressed in U.S. dollars unless otherwise noted. All amounts are expressed on an as-converted from Canadian dollar to U.S. dollar basis are calculated using the conversion rate as of December 31, 2018 unless otherwise noted.

Item 1. Business

Overview

We are a clinical-stage biopharmaceutical company focused on developing innovative products for the treatment of urological diseases. We are headquartered in San Diego, California and our common shares currently trade on The Nasdaq Capital Market. We are currently developing topsalysin (PRX302) as a treatment for clinically significant localized prostate cancer and as a treatment for the lower urinary tract symptoms of benign prostatic hyperplasia, or BPH, commonly referred to as an enlarged prostate. Topsalysin, a first-in-class, pore-forming protein, is a highly ablative agent that is selective and targeted in that it is only activated by enzymatically active prostate specific antigen, or PSA, which is found in high concentrations around prostate tumor cells and in the transition zone of the prostate. In 2004, we licensed exclusive rights to topsalysin from UVIC Industry Partnerships Inc., or UVIC, and The Johns Hopkins University, or Johns Hopkins, for the treatment of prostate cancer and in 2009, we licensed exclusive rights to topsalysin from UVIC and Johns Hopkins for the treatment of the symptoms of BPH. In April 2010, we entered into an exclusive license agreement with Kissei Pharmaceuticals Co., Ltd., or Kissei, pursuant to which we granted Kissei the right to develop and commercialize topsalysin in Japan for the treatment of the symptoms of BPH, prostate cancer, prostatitis or other diseases of the prostate.

Topsalysin, a genetically modified recombinant protein, is delivered via ultrasound-guided injection directly into the prostate. This membrane-disrupting protein is selectively activated by enzymatically active PSA, which is found in high concentrations around prostate tumor cells and in the transition zone of the prostate, leading to localized cell death and tissue disruption without damage to neighboring tissue and nerves. This targeted method of administration limits potential for systemic exposure of topsalysin, together with topsalysin's specific mechanism of action, (activation only by enzymatically active PSA found within the prostate. PSA in circulation is no longer enzymatically active) is thought to contribute to the tolerability and safety profile observed to date.

We have recently completed a multicenter, open-label Phase 2b clinical trial to confirm the dose and optimize the delivery of topsalysin for the treatment of clinically significant localized prostate cancer. The study utilized commercially available software to co-register previously obtained multi-parametric magnetic resonance imaging, or mpMRI, images of a patient's prostate to real time 3D ultrasound images to target the delivery of topsalysin directly into and around a pre-identified clinically significant tumor. A clinically significant tumor that warranted treatment was defined as either a Gleason score 6 (pattern 3+3) and greater than or equal to 6 mm up to 10 mm, Maximum Cancer Core Length, or MCCL, or a Gleason score 7 (pattern 3+4 or 4+3) and lesser than or equal to 10 mm MCCL. The Gleason grading system is used to provide a prognosis of the identified cancer by assigning a Gleason Score and pattern. A high Gleason score indicates aggressive cancer, with a Gleason Score 6 generally representing low risk disease, Gleason 7 intermediate risk and Gleason 8-10 high risk disease.

The primary objective of the trial was to evaluate the safety and tolerability of a single administration of topsalysin, when used to focally ablate a histologically-proven, clinically significant lesion in patients with low-to-intermediate localized prostate cancer. A total of 38 patients with a pre-identified clinically significant lesion received a single administration of topsalysin at eight clinical trial sites located in the United Kingdom and United States. A review of the safety data from 38 patients, indicates that a single administration of topsalysin continues to appear safe and well-tolerated by patients. Adverse events considered related to topsalysin were typically mild and typically occurred and resolved within one day of the administration. In addition, urine function was preserved, there was no sexual dysfunction, no hypersensitivity reactions or other serious systemic reactions considered related to topsalysin after a single administration.

A secondary objective of the trial was to evaluate the efficacy of a single administration of topsalysin to selectively target and focally ablate a pre-identified lesion. Six months after the administration of topsalysin, 37 out of 38 patients underwent a targeted biopsy of the treated lesion with one patient having been lost to follow-up following re-location. The six-month biopsy results demonstrated that 27% of patients (10/37) achieved a clinical response, defined in this trial as no detectable tumor on targeted biopsy of the treated lesion or a sufficient reduction to deem the lesion clinically-insignificant (cancer lesion of Gleason Score 6 (pattern 3+3) and a maximum cancer core length, or MCCL, of less than 6 millimeters).

We believe the safety and biopsy data from the first administration of topsalysin supports moving forward with a single Phase 3 registration trial using a single administration of topsalysin. We expect to obtain regulatory guidance on our design for a Phase 3 registration trial in the first half of 2019.

Another important objective for this Phase 2b clinical trial was to evaluate for the first time the safety of re-administering topsalysin, and to determine if additional clinical benefit could be observed, as assessed by targeted biopsy six months after a second administration of topsalysin. To be eligible to receive a second administration, patients must not have experienced any clinically-significant adverse events attributable to either topsalysin or the injection procedure. Additionally, patients must have demonstrated evidence of a response to the first treatment with topsalysin, either through a reduction in lesion size, Gleason pattern, or MCCL. No patients who had a complete ablation following the first dose received a second administration.

A review of the safety data from a total of eleven patients who received a second administration indicates that a second dose appears to be both safe and well-tolerated by patients. There were no adverse events considered related to topsalysin that were experienced by more than one patient following the second administration. The adverse events that were considered related to topsalysin were typically mild and resolved within two days. Importantly, no hypersensitivity reaction or other serious systemic reactions to topsalysin were observed. Urine function was preserved and there were no reports of sexual dysfunction related to topsalysin. As previously reported, one patient who received a second dose unfortunately experienced a serious adverse event of sudden cardiac death which, following a thorough review of medical records, serology results and autopsy findings, was considered unlikely related to topsalysin or the injection procedure by both the investigator and us.

Based on the review of the six-month biopsy results following the second administration of topsalysin, we have concluded that there appears to be no additional clinical benefit gained with a second administration as given in the Phase 2b trial. We are reviewing the decision to include a second administration of topsalysin in any future clinical studies.

We have also completed the first of two Phase 3 clinical trials that we believe would be required to obtain marketing approval for topsalysin for the treatment of the symptoms of BPH. In October 2013, we initiated our first Phase 3 clinical trial, which we refer to as the "PLUS-1" trial, of topsalysin for the treatment of the lower urinary tract symptoms of BPH. The Phase 3 "PLUS-1" trial was an international, multicenter, randomized, double-blind, and vehicle-controlled trial to assess the efficacy and safety of a single intraprostatic administration of topsalysin (0.6 µg/g prostate) for the treatment of the lower urinary symptoms of BPH. Patients were randomized on a 1:1 ratio to either topsalysin or vehicle-only injection, and then monitored for one year. A total of 479 patients with moderate to severe BPH were enrolled and randomized by September 2014. On November 10, 2015, we announced final results from this trial. Topsalysin demonstrated a statistically significant improvement in International Prostate Symptom Score, or IPSS, total score from baseline over 12 months compared to the vehicle-only control group (7.60 vs. 6.58 point overall improvement; $p = 0.043$), the primary endpoint of the trial. IPSS is a patient recorded, composite assessment that takes into account factors such as ability to empty the bladder, frequency of urination, intermittency of urination, urgency of urination, weak strength of urine stream, straining while urinating, and having to urinate multiple times at night after going to bed. Topsalysin continues to demonstrate a favorable safety profile, with no evidence of any treatment related sexual or cardiovascular side effects.

We are not currently planning on initiating additional clinical trials, including a potential registration trial in localized prostate cancer or a second Phase 3 trial in BPH, unless we obtain additional funding or secure a development partner to fund such new clinical trials. There can be no assurance that such funding or a development partner will be available on acceptable terms or at all. Further, we cannot currently estimate when the clinical development required to seek the regulatory approvals needed to commercialize topsalysin for the treatment of clinically significant localized prostate cancer or the treatment of the symptoms of BPH will be completed.

Topsalysin - Mechanism of Action

Topsalysin is a genetically altered form of the naturally occurring protein proaerolysin. In nature, proaerolysin is produced by *Aeromonas* bacteria, which are commonly found as a contaminant in fresh water and fresh water fish. We have altered the sequence encoding the bacterial protein so that topsalysin is only activated by enzymatically active PSA (as shown in the figure below), an enzyme that is produced in large quantities in the prostate of men with prostate cancer and BPH.

Topsalysin binds to the GPI-anchored receptors on the cell surface of prostate cells. Once activated by PSA, topsalysin combines with other activated topsalysin molecules, forming stable transmembrane pores that induce cell death. Topsalysin has not been detected in plasma following injection into the prostate. The prostate specific activation of topsalysin by enzymatically active PSA thus limits exposure of non-prostate tissues to the drug's activity, contributing to the safety of the therapy.

The mechanism of action is shown in the figure below.

Topsalysin Mechanism of Action

Background on Clinically Significant Localized Prostate Cancer

Prostate cancer is the second most common form of cancer in men in the United States. According to the National Cancer Institute, there were approximately 165,000 new cases of prostate cancer in the United States identified in 2018 with approximately 78% of patients diagnosed with localized disease (disease that has not progressed beyond the confines of the prostate). In the United States, approximately 29,000 were expected to die from prostate cancer in 2018.

Prostate cancer grows very slowly and research has shown that, in many cases, patients with early low risk localized disease have a low likelihood of the cancer spreading beyond the confines of the prostate. These patients may elect to undergo active surveillance, which does not offer any therapeutic benefit but means that their doctor will continue to monitor the patient (typically PSA levels, digital rectal exams and periodic or as indicated biopsies) for any progression of disease. The information collected by the doctor during active surveillance is used to determine if a patient can remain in active surveillance or should undergo treatment. The complex psychological impact that results from a cancer diagnosis is demonstrated by a significant proportion of men (about 10% in most studies) electing to undergo treatment, even though they have had no evidence of biochemical or histopathological progression of their disease during active surveillance.

Current Therapies for Localized Prostate Cancer

Patients with localized prostate cancer who elect to treat their prostate cancer have traditionally been offered radical treatments in the form of surgery to remove the entire prostate and/or whole gland radiation. Potential side effects and toxicities from radical treatments can be significant and permanent. Men who have undergone radical treatments have experienced the following side effects and toxicity rates: erectile dysfunction 30% - 90%, incontinence 5% - 20% and rectal toxicity (which could include proctitis (inflammation of the rectum) with bleeding and bowel problems such as diarrhea) 5% - 20%.

The increasing use of multi-parametric magnetic resonance imaging, or mpMRI, of the prostate and advances in software to co-register previously obtained mpMRI images with live 3D ultrasound images enables physicians to more accurately target their prostate biopsies. Consequently, it is increasingly possible to more confidently identify men with clinically significant lesions. This enables physicians and patients to make a more informed decision about the clinical significance of their disease and whether their disease is at a stage that requires treatment. If it is agreed that treatment is appropriate some patients may be a candidate for targeted focal therapy rather than radical therapies. The objective of targeted focal therapy is to remove the significant disease while preserving as much of the prostate as possible thereby potentially avoiding many of the complications and side effects associated with the radical whole gland treatments. There are several focal targeted therapies currently being offered to patients such as targeted laser ablation, high-intensity focused ultrasound, cryoablation, radiofrequency ablation and photodynamic therapy each with the aim of reducing the treatment impact to the surrounding anatomical structures, potentially leading to lower rates of side effects while retaining the cancer control benefits that the whole gland radical treatments offer. This focal targeted approach to the treatment of prostate cancer is consistent with the management of almost all other solid organ cancers (breast, kidney, liver and pancreas) in which organ preservation is fundamental to functional preservation.

Topsalysin for the Targeted Focal Treatment of Clinically Significant Localized Prostate Cancer

The intraprostatic injection of topsalysin represents a highly targeted approach for potentially treating clinically significant localized prostate cancer that is confined within the encapsulated prostate gland for two reasons:

- a targeted focal delivery of an intraprostatic injection of topsalysin directly into and around a pre-identified tumor(s) within the prostate is now possible; and
- topsalysin has a highly targeted mechanism of action, activated specifically only within the prostate.

Using advancements in MRI and 3D ultrasound imaging, physicians are able to deliver the injection of topsalysin directly into the tumors located within the prostate. The increased use of mpMRI and advances in software to co-register the mpMRI images with live 3D ultrasound images also means that physicians are now able to locate tumors within the prostate and take more accurate biopsies from a patient, enabling the diagnosis of clinically significant lesions. These technical advances are enabling physicians and patients to make a more informed decision about the clinical significance of their disease and whether their disease requires radical treatment or they would be candidates for active surveillance. In addition, these advances make it possible to identify patients with clinically significant lesions that could be candidates for targeted ablation with a focal therapy. The targeted focal treatment of localized prostate cancer is consistent with the treatment approach frequently used for other solid tumors such as breast and liver cancer, where the objective is to remove the tumor and preserve as much of the organ as possible.

The mechanism of action of topsalysin allows for a highly targeted therapeutic activity in localized disease. Topsalysin is only activated in the presence of enzymatically active PSA which is found surrounding prostate cancer lesions. Therefore, we believe topsalysin has the potential to provide a focal targeted therapy for the ablation of localized prostate cancer while potentially avoiding many of the complications and side effects associated with radical treatments.

Background on BPH

BPH is a non-cancerous enlargement of the prostate gland that commonly affects men who are age 50 and older. BPH causes a restriction in urine flow from the urethra resulting in lower urinary tract symptoms, or LUTS. BPH, and its associated clinical manifestations of LUTS, is one of the most common medical conditions of aging men in the United States, with approximately 70% men aged 60-69 years and 80% of men older than the age of 70 being affected by BPH. The number of men with symptoms of BPH is expected to increase as the male population ages. Our market research suggests that as many as 36 million men in the United States are affected by BPH with approximately five million of these men suffering from bothersome symptoms. Symptomatic BPH greatly diminishes a patient's quality of life. It causes a significant array of LUTS, including increased urinary frequency, urgency to urinate, frequent night-time urination, weak urine stream, and incomplete emptying of the bladder. In addition, men with BPH symptoms are predisposed to a higher risk of urinary tract infections, urinary stone formation, bladder damage, and in very late stage and/or unattended cases, renal damage.

Current Therapies for BPH

Physicians and patients choose treatments for the symptoms of BPH primarily based on the severity of symptoms, the patient's quality of life and the presence of other medical conditions. Treatment options include watchful waiting, lifestyle changes, oral medications, minimally invasive surgical therapies or more aggressive surgical therapies, such as transurethral resection of the prostate, or TURP, or open prostatectomy. Our market research indicates that approximately three million men in the United States are taking oral drug therapy and there were approximately 200,000 surgical procedures for the treatment of the symptoms of BPH conducted in 2011.

The effectiveness of treatments for the symptoms of BPH is measured by IPSS and improvement in peak urine flow rate, or Qmax. IPSS is a patient recorded, composite assessment that takes into account factors such as ability to empty the bladder, frequency of urination, intermittency of urination, urgency of urination, weak strength of urine stream, straining while urinating, and having to urinate multiple times at night after going to bed. This index is measured on a 0 to 35 scale with 0 being defined as having no problems and 35 being defined as the high end of severe symptoms. Patients are typically considered to have mild symptoms with IPSS of 1 to 7, moderate symptoms with scores of 8 to 19 and severe symptoms with scores of 20 to 35. An improvement of 3 points in IPSS is generally considered clinically meaningful by urologists. IPSS is a validated primary clinical endpoint used to assess the treatment benefit in BPH clinical trials and has served as the primary efficacy endpoint for the approval of many products for the treatment of the symptoms of BPH. An approximate 2 point difference in IPSS improvement between active and control has historically been utilized by the FDA to approve oral therapies, although the FDA has not provided guidance that a 2 point difference is required for approval of treatment for the symptoms of BPH.

Oral Drug Therapy

The most common form of therapy for men experiencing mild to moderate LUTS associated with BPH is oral drug therapy. Current classes of oral medications available for treatment of the symptoms of BPH include alpha-blockers, 5-alpha-reductase inhibitors, or 5-ARIs, a combination of an alpha-blocker and 5-ARI, and a phosphodiesterase Type 5 inhibitor, or PDE5. An alpha-blocker provides rapid relief of BPH symptoms but does not prevent continued growth of the prostate. Examples of alpha-blockers include terazosin, doxazosin, tamsulosin, alfuzosin, and silodosin. Frequently reported side effects of alpha-blockers include hypotension, or low blood pressure, dizziness and feeling of weakness. 5-ARIs, such as finasteride and dutasteride, reduce the size of the prostate and thus provide symptom relief. It may take up to six months from starting treatment with a 5-ARI for the prostate to reduce in size and for patients to experience the benefit of treatment. Side effects include sexual dysfunction. In addition, tadalafil (marketed by Eli Lilly as Cialis®), a PDE5 inhibitor (a class of drugs typically prescribed for erectile dysfunction), was shown to improve IPSS after four weeks of dosing and has been approved for treatment of the symptoms of BPH. Headache and dyspepsia, or indigestion, are the most commonly observed side effects of Cialis®, which is not recommended for use in combination with an alpha-blocker because of the risk of hypotension.

Many men will discontinue oral drug therapy due to inadequate response and/or the side effects mentioned above. Another drawback of the currently available oral therapies is the necessity of taking one or more pills daily. Published patient survey data (N=2,166) suggests that as many as 57% of patients taking oral drug therapy discontinue use within the first three years.

In previously completed clinical trials, each of these classes of oral medications has typically produced approximately 3 to 6 point reductions in IPSS, but the actual magnitude of treatment benefit observed compared to placebo is generally two to three points.

Minimally Invasive Surgical Therapies

Minimally invasive surgical therapies used to treat the symptoms of BPH include transurethral microwave thermotherapy, or TUMT, transurethral needle ablation, or TUNA, Urolift®, a system which lifts and holds the enlarged prostate tissue away from the urethra, and green laser treatment, which delivers high energy to ablate the prostatic tissue as an alternative to TURP. These treatments, frequently referred to as MIST, are generally less effective than surgical procedures in reducing the size of the prostate gland and often require retreatment within three years. However, these treatments may require catheterization and are still associated with pain and the potential for complications such as bleeding and long-lasting side effects such as urinary incontinence and sexual dysfunction, including erectile dysfunction and retrograde ejaculation (semen flowing backward into the bladder). A new TUNA, known as the Rezum System, was approved in 2015. Rezum delivers radiofrequency generated thermal therapy in the form of water vapor via a transurethral needle. Studies of MIST procedures have shown varying improvements in IPSS, with TUNA and TUMT showing improvement in IPSS of approximately 10 to 13 points.

Other Surgical Options

Surgical procedures such as TURP typically reduce the size of the prostate gland and relieve the pressure on the urethra by ablating the prostate tissue that blocks the flow of urine. Studies of surgical procedures have generally shown reductions in IPSS of approximately 16 points. TURP is performed under spinal or general anesthesia, which carries the risk of side effects. TURP may result in nerve damage, bleeding (sometimes requiring transfusion), and long-lasting side effects, such as urinary incontinence and sexual dysfunction, including erectile dysfunction and retrograde ejaculation.

Topsalysin for the Treatment of the Symptoms of BPH

In our completed Phase 3 clinical trial, topsalysin significantly improved symptoms of BPH through 12 months of follow-up after a single treatment. Topsalysin is designed to be a safe, simple and convenient treatment that provides rapid and sustained relief of BPH symptoms. It is delivered through a targeted injection into the prostate, precisely ablating the prostate tissue without damaging neighboring tissue and nerves. This method of administration limits the circulation of the drug in the body and we believe that this limited systemic exposure to the drug, together with how the drug is activated in the body, greatly diminishes the risk of side effects.

The injection of topsalysin is individualized to each patient based on the size of the prostate and the drug is delivered in a procedure that can be performed in a urologist's office. The entire process can be completed during a short office visit, and the actual injection of the drug into each of the two lobes of the prostate takes approximately four minutes. A physician administering topsalysin may elect to administer a local anesthetic before injection. Most urologists are familiar with the transrectal route of administration, as it is the same method urologists use to take biopsies of the prostate.

Market research we conducted with 100 urologists in 2012 has shown that topsalysin compares favorably to both oral therapies and procedures on a number of key attributes related to effectiveness, safety, tolerability, and burden placed on the patient. Specifically, when shown results from our Phase 2b clinical trial, the physicians viewed topsalysin as being more effective and having a better side effect profile than currently available oral drugs. Administration of topsalysin was also perceived as more effective, safer, and easier to perform than MIST procedures, TUNA and TUMT. When compared to TURP surgery, topsalysin was also perceived as safer and easier to administer. In this market research, physicians indicated a willingness to consider topsalysin as an alternative to both oral therapies and surgical procedures and also viewed topsalysin as a potential new choice for men who have discontinued oral therapy and are not willing to undergo a surgical procedure.

Clinical Overview

To date, we have completed nine clinical trials of topsalysin. Five of our completed clinical trials were for the treatment of the symptoms of BPH and four were for the treatment of prostate cancer. In the nine completed clinical trials a total of 365 patients with moderate to severe BPH and 86 patients with prostate cancer have been treated with topsalysin for a combined topsalysin exposure of 451 patients.

We have completed two clinical trials for the targeted focal treatment of localized low to intermediate risk prostate cancer. A single administration of topsalysin continues to appear safe and well-tolerated by patients. Adverse events considered related to topsalysin were typically mild and typically occurred and resolved within a day of administration. In addition, urine function was preserved, there was no sexual dysfunction, no hypersensitivity reactions or other serious systemic reactions considered related to topsalysin after a single administration.

A single administration of topsalysin has also demonstrated an ability to ablate tumor cells as observed on targeted biopsy six months after the targeted treatment of a pre-identified lesion in a patient population with clinically significant localized prostate cancer.

In our Phase 2b clinical trial for the treatment of localized prostate cancer, a review of the safety data from a total of eleven patients who received a second administration indicated that a second dose appears to be both safe and well-tolerated by patients. Based on the review of the six-month biopsy results following the second administration of topsalysin, we have concluded that there appears to be no additional clinical benefit gained with a second administration as given in this Phase 2b trial.

In addition to the two trials in which topsalysin was administered as a targeted focal therapy in patients with low to intermediate risk localized prostate cancer, the Company had previously completed two clinical trials of topsalysin in a different patient population, as a treatment for locally recurrent prostate cancer. The patients in these two small open-label studies were patients who had previously undergone radiation for the treatment of their prostate cancer and showed signs of disease recurrence evidenced by rising levels of PSA. The results from these clinical trials demonstrated that topsalysin was well-tolerated and showed early signs of therapeutic activity following a single intraprostatic treatment.

All of the completed clinical trials of topsalysin for the treatment of the symptoms of BPH have shown clinically meaningful, sustained efficacy with regard to improvement in LUTS, as measured by IPSS and Qmax, the standard measures of the treatment of LUTS for BPH. Topsalysin has been well-tolerated in all completed BPH clinical trials to date. Adverse events in our completed BPH clinical trials were typically mild and transient in nature, limited to local discomfort and irritative urinary symptoms that generally occurred on the same day as topsalysin injection. There have been no drug-related sexual or cardiovascular side effects reported.

Seven clinical trials for topsalysin (four prostate cancer trials and three BPH trials) used the transperineal route of administration for the intraprostatic injection and the two most recent clinical trials in BPH, including our completed PLUS-1 trial, used the transrectal route. The transrectal route appears to be as well tolerated as the transperineal route.

Clinical Development of Topsalysin

Our clinical program for topsalysin is summarized below.

Completed Clinical Development in Prostate Cancer

CLINICAL TRIAL	STATUS	TRIAL DESIGN
PRX302-2-08 Phase 2b Dose Confirmation and Delivery Optimization Trial	Completed	Phase 2b open-label 6 to 12 month trial with topsalysin in patients who have histologically proven, clinically significant localized prostate cancer to confirm the dose and optimize the delivery of a single and potentially a second transperineal intraprostatic treatment of topsalysin Number of patients: 38 Dosing: Varied based upon prostate volume and size of the lesion to be injected, up to 12 ug/gram of prostate and 1,000 ug/gram of lesion
PRX302-2-07 Phase 2a	Completed	Phase 2a open-label 6 month proof of concept trial with topsalysin in patients who had histologically proven, localized low to intermediate risk prostate cancer. 18 patients Dosing: Varied based upon prostate volume and the size of the lesion to be injected but the dose did not exceed 5µg/gm of prostate and when normalized for lesion size up to 1000 ug/gram of tumor lesion
PRX302-1-02 Phase 2a	Completed	Open-label, safety, 12 month dose escalation & volume escalation of a single transperineal intraprostatic treatment of topsalysin in patients who had previously undergone radiation treatment of their prostate cancer 6 patients Dosing: 6.0µg/g, 12.0µg/g of prostate Volume: 20% to 40% of prostate volume
Phase 1	Completed	Open-label, safety, 12 month dose-escalation of a single transperineal intraprostatic treatment of topsalysin in patients who had previously undergone radiation treatment of their prostate cancer 24 patients Dosing: 0.03µg/g of prostate, 0.09µg/g of prostate, 0.3µg/g of prostate, 0.6µg/g of prostate, 1.2µg/g of prostate, 2.1µg/g of prostate, 3.0µg/g of prostate Volume: Fixed at 10% of prostate volume

Plans for Future Clinical Development in Localized Prostate Cancer

CLINICAL TRIAL	STATUS	TRIAL DESIGN
Phase 3	Initiation dependent upon regulatory guidance and receipt of funding to run the study	To be confirmed following regulatory input: Dosing: Varied based upon prostate volume and size of the lesion to be injected up to 1,000 ug/gram of lesion, but the dose will not exceed 12 ug/gram of prostate

Clinical Development in Localized Prostate Cancer

Phase 2b Open-Label Clinical Trial in Localized Prostate Cancer

The primary objective of this trial was to evaluate the safety and tolerability of a single, and if applicable, a second administration of topsalysin, when used to focally ablate a histologically-proven, clinically significant lesion in patients with low-to-intermediate localized prostate cancer.

In the Phase 2b clinical trial, 38 patients with pre-identified, localized prostate cancer received a single administration of topsalysin at eight clinical trial sites in the United Kingdom and United States. Six months after administration, patients received a follow-up targeted biopsy of the treated lesion. Six-month follow-up biopsies have been undertaken and evaluated from 37 of 38 patients treated with a single administration of topsalysin, with one patient having been lost to follow-up following re-location.

Final Safety and Biopsy Results from a Single Administration of Topsalysin:

To date, a single administration of topsalysin continues to appear safe and well tolerated by patients with no new safety signals. No hypersensitivity reactions or other serious systemic reactions to study medication were observed after a single administration. Analysis of the safety data from all 38 patients receiving a single administration of topsalysin indicate the following adverse events occurred in more than one patient and were considered related to topsalysin: dysuria (3 patients), urinary retention (3 patients), proctalgia (2 patients), perineal pain (2 patients), nocturia (2 patients), micturition urgency (2 patients) and strangury (2 patients). Topsalysin related adverse events were typically considered mild and typically resolved within one day. One event of micturition urgency was considered severe and resolved the same day, two events were considered moderate in severity, one event of perineal pain which resolved within a day and one event of urinary retention was considered moderate and the event was considered resolved after the patient underwent a transurethral resection of the prostate. One event of stranguary considered related to topsalysin and mild was reported as a serious adverse event (SAE) because the patient was hospitalized overnight for monitoring as was the practice at the site in the UK where the patient had been treated. The event of stranguary resolved the next day and the patient was released from the hospital.

A secondary objective of this trial was to evaluate the efficacy of a single administration of topsalysin to selectively target and focally ablate a pre-identified lesion.

A single administration of topsalysin continues to demonstrate an ability to ablate targeted prostate cancer cells. The final six-month biopsy results from 37 patients on whom biopsy data were available indicate that, 27% of patients (10/37) achieved a clinical response, defined in this trial as no detectable tumor on targeted biopsy of the treated lesion or a sufficient reduction to deem the lesion clinically-insignificant (cancer lesion of Gleason Score 6 (pattern 3+3) and a maximum cancer core length, or MCCL, of less than 6 millimeters). This compares favorably to 17% of patients (3/18) moving to clinically insignificant disease in the previously completed Phase 2a proof of concept localized prostate cancer clinical trial. Of the 10 clinical responders in the Phase 2b trial, six patients experienced a complete ablation with no histological evidence of the targeted tumor remaining.

Additionally, the Phase 2b single administration follow-up biopsy data showed that:

- 41% of patients (15/37) experienced a partial response, defined as a reduction in MCCL and/or Gleason pattern, but the targeted lesion was still deemed clinically-significant based on the targeted biopsy; and
- 32% (12/37) of patients did not respond to treatment defined as no change in the targeted lesion or an increase in MCCL and/or Gleason pattern.

We believe the safety and biopsy data from the first administration of topsalysin supports moving forward into potential registration trials. We have begun planning for a Phase 3 clinical trial for topsalysin for the treatment of clinically significant intermediate risk localized prostate cancer and initiation of this clinical trial is subject to receiving additional financing or securing a development partner. We expect to obtain formal regulatory guidance on a design for a Phase 3 registration trial in the first half of 2019.

Results from the Second Administration of Topsalysin

Another important objective for this Phase 2b clinical trial was to evaluate for the first time, the safety of re-administering topsalysin, and to determine if additional clinical benefit could be observed as assessed by targeted biopsy six months after a second -administration of topsalysin. To be eligible to receive a second administration, patients must not have experienced any clinically-significant adverse events attributable to either topsalysin or the injection procedure. Additionally, patients must have demonstrated evidence of a response to the first treatment with topsalysin, either through a reduction in lesion size, Gleason pattern, or MCCL. No patients who had a complete ablation following the first dose received a second administration.

A review of the safety data from the eleven patients who received a second administration indicates that a second dose appears to be both safe and well-tolerated by patients. There were no adverse events considered related to topsalysin that were experienced by more than one patient following the second administration. The adverse events that were considered related to topsalysin were typically mild and resolved within two days. Importantly, no hypersensitivity reaction or other serious systemic reactions to topsalysin were observed. Urine function was preserved and there were no reports of sexual dysfunction related to topsalysin. As previously reported, one patient who received a second dose unfortunately experienced a serious adverse event of sudden cardiac death which, following a thorough review of medical records, serology results and autopsy findings, was considered unlikely related to topsalysin or the injection procedure by both the investigator and Company. There was one event of post procedure perineal pain that was reported as mild and related to topsalysin that was considered a SAE as the patient was administered morphine and admitted to the hospital overnight for observation, as is the practice at the UK site after administering morphine. The event resolved the next morning and the patient was discharged home.

Based on review of the six-month biopsy results following the second administration of topsalysin, we have concluded that there appears to be no additional clinical benefit gained with a second administration as given in this Phase 2b trial. We are reviewing the decision to include a second administration of topsalysin in any future clinical studies.

Phase 2a Proof of Concept Trial in Localized Prostate Cancer

In June 2016, we completed a single-center, open-label Phase 2a proof of concept clinical trial of topsalysin for the treatment of localized low to intermediate risk prostate cancer. We believe that the highly targeted mechanism by which topsalysin selectively destroys prostate tissue in BPH makes topsalysin a potential targeted focal treatment for localized prostate cancer. The clinical trial utilized previously obtained MRI images of each patient's prostate mapped to real time 3D ultrasound to target the delivery of topsalysin directly into and around a pre-identified clinically significant tumor. A clinically significant tumor was defined in our study as, either a Gleason score 6 (pattern 3+3) and >3mm Maximum Cancer Core Length, or MCCL, or Gleason score 7 (pattern 3+4 or 4+3) < 10 mm MCCL, which is thought to have the potential to progress and would therefore warrant treatment. (A Gleason pattern is a grading system utilized to describe how aggressive a prostate tumor is and how likely it is to spread. Generally, there are five recognized Gleason histological patterns and a higher Gleason pattern indicates a more aggressive tumor.) Patients received a transperineal administration of topsalysin under general anesthesia at a dose higher than used in our completed Phase 3 BPH PLUS-1 trial but less than the highest dose used in our previous prostate cancer trial. The primary objective of the trial was to assess the safety and tolerability of topsalysin when used to selectively target and focally ablate a clinically significant tumor. The potential efficacy was evidenced by histological changes, indicating tumor ablation at six months following treatment. The clinical trial was conducted at a single center, the University College London, which is well known for the focal treatment of prostate cancer in the United Kingdom.

A total of 18 patients with localized low to intermediate risk prostate cancer were enrolled in the Phase 2a proof of concept clinical trial. The one-time administration of topsalysin was well tolerated with no serious adverse events and no new safety signals being reported. Topsalysin demonstrated an ability to ablate tumor cells in more than 60 percent of patients (11 of 18 patients) six months after treatment in a patient population with pre-identified, clinically significant prostate cancer.

All 18 patients enrolled completed the study. Biopsy data at six months following treatment showed that:

- Two patients experienced complete ablation of their targeted tumor with no evidence of any tumor remaining at six months;
- Nine patients experienced a partial response, defined as either a reduction in the maximum cancer core length or a reduction in Gleason pattern; and
- Seven patients had no response to treatment.

Phase 2 Open-Label Clinical Trial in Locally Recurrent Prostate Cancer

In September 2009, we completed a Phase 2 clinical trial of topsalysin in six patients with biopsy-proven, locally-recurrent prostate cancer that, following radiation therapy, showed signs of disease progression evidenced by rising levels of PSA. Therapeutic activity in the form of overall decreases in PSA levels and in the number of adenocarcinoma-positive biopsy cores following topsalysin treatment was observed in two of six patients.

Phase 1 Open-Label Clinical Trial in Locally Recurrent Prostate Cancer

In May 2008, we completed a multicenter, open-label, dose-escalation Phase 1 clinical trial of topsalysin in 24 patients in the United States with biopsy-proven, locally-recurrent prostate cancer that, following radiation therapy, showed signs of disease progression evidenced by rising levels of PSA. Elevated and rising levels of PSA can be a sign of the presence or progression of prostate cancer. The primary clinical endpoint of this clinical trial was to examine the safety and tolerability of topsalysin with therapeutic activity as the secondary clinical endpoint. Clinical trial results demonstrated that topsalysin was well-tolerated and showed early signs of therapeutic activity following a single intraprostatic treatment.

No topsalysin treatment-related serious adverse events were reported and the treatment-related adverse effects that were reported were mild and were primarily associated with the injection procedure.

Plans for Future Clinical Development in Localized Prostate Cancer

We believe the safety and biopsy data from the first administration of topsalysin supports moving forward with a single Phase 3 registration trial design using a single administration of topsalysin. We expect to obtain formal regulatory guidance on our design for a Phase 3 registration trial in the first half of 2019.

We are currently not planning on pursuing a Phase 3 registration trial in localized prostate cancer, unless we secure a development partner to fund such new clinical trial or obtain other financing. There can be no assurance that such funding or a development partner will be available on acceptable terms or at all. For that reason, we cannot currently estimate when the clinical development required to seek the regulatory approvals needed to commercialize topsalysin for the treatment of clinically significant localized prostate cancer will be completed.

Clinical Development in BPH

CLINICAL TRIAL	STATUS	TRIAL DESIGN
PLUS-1 Phase 3 Trial #1	Completed	Prospective, randomized, double-blind, placebo-controlled clinical trial of a single transrectal intraprostatic treatment of topsalysin, which will utilize the IPSS outcome measure evaluated at 12 months as the primary endpoint 479 patients, 239 on topsalysin; 240 on vehicle Dosing: 0.6µg/g of prostate Volume: 20% of prostate volume
PRX302-2-03 **TRIUMPH** Phase 2b	Completed	Randomized, double-blinded, placebo-controlled trial of a single transperineal intraprostatic treatment of topsalysin 92 patients; 61 on topsalysin; 31 on vehicle Dosing: 0.6 µg/g of prostate Volume: 20% of prostate volume
PRX302-2-06 **Transrectal Trial** Phase 1/2	Completed	Randomized dose-escalation, multicenter trial of a single transrectal intraprostatic treatment of topsalysin 40 patients; 32 on topsalysin in 4 dosing cohorts; 8 on placebo Dosing: 0.15µg/g of prostate, 0.30µg/g of prostate, 0.60µg/g of prostate, 1.2µg/g of prostate Volume: 20% of prostate volume
PRX302-2-02 Phase 2a	Completed	Open-label, safety, volume escalation clinical trial of a single transperineal intraprostatic treatment of topsalysin 18 patients Dosing: 0.3µg/g of prostate, 0.6µg/g of prostate, 0.9µg/g of prostate Volume: 10 to 30% of prostate volume
PRX302-2-01 Phase 1	Completed	Open-label, safety, dose-escalation clinical trial of a single transperineal intraprostatic treatment of topsalysin 15 patients Dosing: 0.025µg/g of prostate, 0.072µg/g of prostate, 0.25µg/g of prostate, 0.35µg/g of prostate Volume: 1.5 to 2.0 mL

Plans for Future Clinical Development in BPH

CLINICAL TRIAL	STATUS	TRIAL DESIGN
Phase 3 Trial #2	Planned but initiation dependent upon receipt of funding to run the study	Prospective, randomized, double-blind, placebo-controlled clinical trial of a single transrectal intraprostatic treatment of topsalysin Dosing: 0.6µg/g Volume: 20% of prostate volume
Open-Label Safety Study Phase 3	Planned but initiation dependent upon receipt of funding to run the study	Safety of repeat dose and long-term safety of transrectal intraprostatic treatment of topsalysin Approximately 100 patients Dosing: 0.6µg/g Volume: 20% of prostate volume

Completed Clinical Development in BPH

PLUS-1 Randomized, Double-Blind, Placebo-Controlled Transrectal Route of Injection Clinical Trial

In October 2013 we initiated our first Phase 3 clinical trial, which we refer to as the "PLUS-1" trial, of topsalysin for the treatment of the lower urinary tract symptoms of BPH. The Phase 3 "PLUS-1" trial is an international, multicenter, randomized, double-blind, and vehicle-controlled trial to assess the efficacy and safety of a single intraprostatic administration of topsalysin (0.6 µg/g prostate) for the treatment of the symptoms of BPH. Patients were randomized in a 1:1 ratio to either topsalysin or vehicle-only injection, and then monitored for one year. A total of 479 patients with moderate to severe BPH were enrolled and randomized by September 2014. The 52-week completion rate was 91.9%, with a similar number of premature withdrawals from study for the topsalysin group (8.8%) vs. the vehicle group (7.5%). On average, the injection itself was completed in less than four minutes. This Phase 3 clinical trial used the IPSS total score change from baseline over 52 weeks using the repeated measures linear mixed model as the primary endpoint. Secondary endpoints included Qmax (maximum urine flow) change from baseline over 52 weeks.

Treatment groups were well balanced at baseline, including average IPSS total score (21.2 points both groups), Qmax (maximum urine flow) (9.5 mL/sec both groups), total prostate volume (49.8 mL for topsalysin vs. 48.1 mL vehicle), prior BPH treatment (55.2% topsalysin vs. 55.1% vehicle), and quality of life (4.5 points both groups, "mostly dissatisfied" to "unhappy" with current urinary condition).

The results of this trial were:

- *Topsalysin demonstrated statistical significance over vehicle* – The primary efficacy endpoint of the IPSS total score change from baseline over 52 weeks was analyzed, per guidance from the FDA, using the repeated measures linear mixed model applied to the modified intent-to-treat population of every patient randomized and dosed with study drug. Topsalysin demonstrated a statistically significant improvement in IPSS total score from baseline over 12 months compared to the vehicle-only control group (7.60 vs. 6.58 point overall improvement; $p = 0.043$), the primary endpoint of the study.

- *Improvement was clinically meaningful, rapid and sustained* – In a secondary efficacy analysis of IPSS total score using an ANCOVA model and last observation carried forward, or LOCF, to impute missing post-baseline data, the improvement in IPSS for topsalysin was well sustained over the 52 weeks following the single administration. The maximal effect of 8.31 points improvement in IPSS vs vehicle 6.89 points ($p = 0.012$) was achieved at Week 18 with 8.04 points of improvement for topsalysin still remaining at Week 52 vs 6.64 points for patients treated with vehicle only ($p = 0.022$) representing an end-of-study preservation of 97% of the peak benefit.

- *Improvement in Qmax* – Secondary efficacy endpoints included analysis of Qmax (maximum urine flow) change from baseline over 52 weeks by the repeated measures linear mixed model, which showed overall improvement of 1.77 mL/sec for topsalysin, representing a statistical trend that narrowly missed statistical significance ($p = 0.055$) compared to the vehicle group.

- *Improvement in Quality of Life was clinically meaningful* – An additional efficacy endpoint was the patient self-assessment of disease-specific Quality of Life. On the 0 to 6 point Quality of Life (QOL) from the IPSS questionnaire, the topsalysin average change from the 4.5 point baseline was a sustained 1.6 to 1.7 points improvement from Weeks 18 through 52, which was statistically significantly superior to vehicle for every post-baseline visit beginning at Week 18 (reaching $p = 0.004$).

- *Topsalysin was well-tolerated* – Topsalysin treatment was generally well-tolerated, and no patient was withdrawn from the trial or had their study drug injection altered because of an adverse event, or AE. The safety profile was consistent with that reported in the TRIUMPH Phase 2 trial. Adverse events occurring in ≥5% of patients treated with topsalysin regardless of assessed relatedness to study treatment are set forth in the table below. These AEs are not unexpected manifestations of the intraprostatic cellular destruction and resultant inflammation integral to the topsalysin mechanism of action. The median duration for each of these adverse events was typically less than one day. In general, these adverse events were mild or moderate, transient, began within the first few days after treatment (primarily on the same day as the study drug injection) and were resolved without consequences.

Adverse Events Occurring in ≥5% of Subjects treated with topsalysin

Adverse Event[(1)]	Vehicle (N=240) n (%)		Topsalysin (N=239) n (%)	
Dysuria (e.g., burning, pain, or discomfort on urination)	20	(8.3)	48	(20.1)
Haematuria (microscopic or visible red blood cells in urine)	36	(15.0)	45	(18.8)
Pollakiuria (frequent urination)	14	(5.8)	23	(9.6)
Pyrexia (fever)	10	(4.2)	21	(8.8)
Perineal Pain	13	(5.4)	21	(8.8)

(1) (MedDRA Preferred Terms)

The incidence of serious adverse events, or SAEs was similar in both treatment groups. There were two SAEs assessed by the investigator as at least possibly related to treatment for topsalysin and one such SAE for vehicle. The topsalysin-related SAEs were moderate events of "acute non-infectious prostatitis" and "fever following prostate procedure" not unexpected manifestations of the intraprostatic cellular destruction and resultant inflammation integral to the topsalysin mechanism of action. The vehicle-related SAE was a mild event of "urinary tract infection." There were no treatment related sexual dysfunction or cardiovascular side effects reported in this clinical trial.

In order to seek regulatory approval for topsalysin for the treatment of the symptoms of BPH, we would be required to conduct a second Phase 3 clinical trial and we do not expect to commence any additional Phase 3 clinical trials unless we obtain the funding or secure a development partner to fund such trial.

TRIUMPH Phase 2b Randomized, Double-Blind, Placebo-Controlled Clinical Trial

In 2010, we completed TRIUMPH, a multicenter, randomized, double-blinded, placebo-controlled Phase 2b clinical trial of topsalysin in 92 patients with moderate to severe BPH symptoms who were randomized to topsalysin or vehicle on a 2:1 ratio. The primary objective of this clinical trial was to evaluate the effect on symptoms of BPH of topsalysin versus placebo. Patients randomized to placebo, which is referred to as the vehicle, were administered by injection an equivalent volume of phosphate-buffered saline that did not include active drug product. The patient population that we used to evaluate efficacy in this clinical trial, as defined by the clinical trial protocol, was the efficacy evaluable, or EE, population of patients, which was defined as those 73 patients who (1) received the full treatment, (2) completed three month assessments, and (3) had no major protocol violation, as determined by a blinded, independent review panel of urology experts. The intent-to-treat, or ITT, and safety patient populations consisted of all 92 patients who received any study drug. Our efficacy analyses in this clinical trial used the LOCF method to impute missing post-baseline data.

The results of this clinical trial were:

- *Topsalysin improved LUTS due to BPH* – We achieved the primary endpoint of this clinical trial, which was a statistically significant improvement in IPSS at three months following injection for patients treated with topsalysin versus patients who received vehicle. Topsalysin treatment resulted in a 9.1 average reduction of IPSS, as compared to a 5.8 average reduction in patients who received vehicle (p=0.040).

- *Improvement was clinically meaningful, rapid and sustained* – Improvement in IPSS was observed as early as 14 days following injection and was sustained through the twelfth month of observation. This improvement in IPSS was clinically meaningful, and superior to vehicle.

- *Improvement in Qmax* – Topsalysin treatment resulted in an approximately 3.1 mL/sec average increase in Qmax at three months, as compared to 1.3 mL/sec for vehicle (p=0.047). The improvement in Qmax for topsalysin was apparent from the first post-baseline assessment and sustained through the twelfth month of observation.

- *Topsalysin was well-tolerated* – The topsalysin injection was well-tolerated by patients in this clinical trial. The most common adverse events that were potentially attributable to topsalysin are set forth in the table below. These adverse events generally are not unexpected manifestations of the intraprostatic cellular destruction and inflammation integral to the topsalysin mechanism of action. The median duration for each of these adverse events was typically less than two days. In general, these adverse events were mild and transient, began within the first few days after treatment (primarily on the same day as the study drug injection) and were resolved without further complications.

There were no drug-related erectile dysfunction or cardiovascular side effects reported in this clinical trial. In addition, 16.1% of patients in the vehicle group dropped out of the study due to lack of efficacy and the need for alternative therapy as compared to 3.3% of patients in the active group.

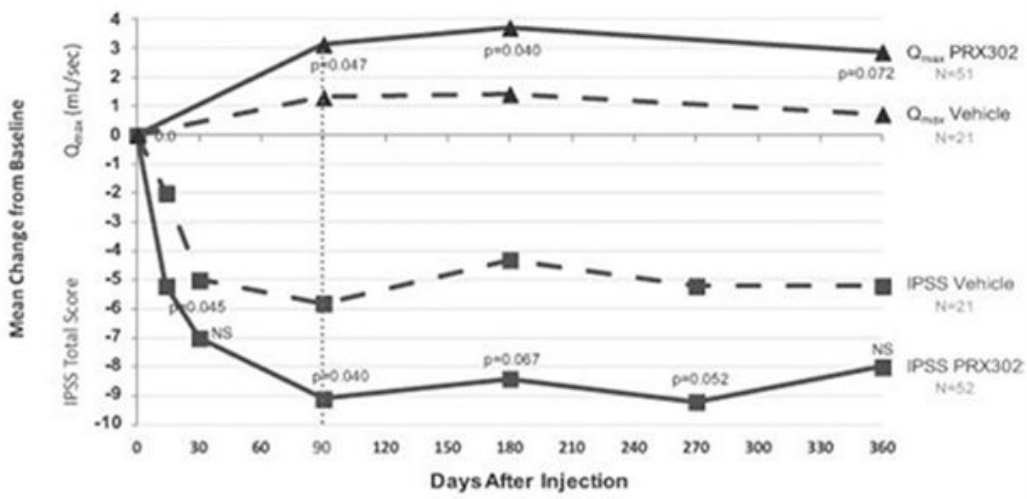
Adverse Events Occurring in >5% of Subjects treated with topsalysin (ITT Population)

Adverse Event[(1)]	Vehicle (N=31) n (%)	Topsalysin (N=61) n (%)
Hematuria, or presence of red blood cells in urine	11(35.5)	18(29.5)
Dysuria, or painful urination	2(6.5)	17(27.9)
Pollakiuria, or increased frequency of urination	5(16.1)	14(23.0)
Micturition Urgency, or urgency of urination	3(9.7)	13(21.3)
Perineal Pain	0(0.0)	7(11.5)
Vertigo	2(6.5)	4(6.6)
Malaise	0(0.0)	4(6.6)

(1) (MedDRA Preferred Terms)

In summary, these results demonstrate that topsalysin is able to maintain a treatment benefit based on both measures of efficacy, IPSS and Qmax, which is clinically meaningful and sustained for the 12 months of monitoring in this clinical trial.

IPSS and Qmax in the Phase 2b BPH TRIUMPH Clinical Trial
N=73 Efficacy-Evaluable Patients using LOCF; 52 topsalysin and 21 Vehicle



P-values represent the likelihood that clinical trial results were due to random statistical fluctuations rather than true cause and effect. The lower the p-value, the more likely there is a true cause and effect relationship.

In our studies and other intraprostatic injection studies, vehicle response rates of 5 to 7 point improvements in IPSS have been observed. We believe that the vehicle response is due in part to the fluid injection potentially ablating prostate cells.

Although the clinical trial protocol did not specify an ITT population analysis, an improvement of 8.2 points in IPSS was observed in the active group of the ITT population. This was not statistically significant when compared to an improvement in the vehicle group of 7.2 points. Thirteen percent of the active group and 23% of the vehicle group were included in the ITT population but not included in the EE population because they were deemed major protocol violators based on confounding factors. Examples of confounding factors were taking prohibited medications, including other medications to treat the symptoms of BPH, or undergoing prohibited procedures during the clinical trial.

Transrectal Phase 1/2, Randomized, Double-Blind, Placebo-Controlled Clinical Trial in BPH

In March 2012, we completed dosing in a multicenter, randomized, double-blinded, vehicle-controlled Phase 1/2 clinical trial of topsalysin using the transrectal route of administration for the intraprostatic injection of topsalysin. Each of the previous clinical trials used transrectal ultrasound to guide the intraprostatic injection, but this clinical trial was the first to use the rectum as the route of administration rather than passing the needle through the perineum. The transrectal route has the advantage of being very similar to the routine prostate biopsy procedure, and therefore requires little extra training for the practicing urologist. The primary endpoint of this clinical trial was to evaluate the three-month safety and tolerability of escalating doses of topsalysin. The safety data from this new route of administration of topsalysin were needed for a comparison with the safety profile obtained from our previously-conducted Phase 1 and 2 clinical trials, which utilized a transperineal route of administration.

We enrolled 40 patients with moderate to severe BPH symptoms in this clinical trial who were randomized to topsalysin or placebo in a 4:1 ratio within each of the four escalating dose cohorts. All patients in this clinical trial received a single, transrectal, intraprostatic treatment of study drug or vehicle at 20% of the patient's prostate volume, in four sequential cohorts according to escalating topsalysin dose: 0.15, 0.30, 0.60, and 1.20 μg/g prostate. Dose escalation decisions were guided by an independent data monitoring committee for each new cohort after all patients in the previous cohort had been followed for at least 15 days after study drug administration.

The results of this clinical trial showed that topsalysin was generally well-tolerated. The side effect profile in this transrectal clinical trial was consistent with the side effects reported in the previous, transperineal topsalysin clinical trials, indicating that topsalysin injection by the transrectal route was tolerated at least as well as the transperineal route. There was one serious adverse event that was deemed by the investigator to be related to injection of topsalysin in this clinical trial. This serious adverse event of urinary retention required an indwelling catheter followed by TUNA. There were no reports of sepsis in this clinical trial. With the switch to a transrectal route of administration, there is a potential risk of sepsis as currently the rate of sepsis with prostate biopsies in the United States is approximately 3-5%. However, prostate biopsies involve as many as 20 punctures and a large needle, whereas topsalysin administration requires only two punctures with a smaller needle. There were no drug-related erectile dysfunction or cardiovascular side effects reported in this clinical trial.

The small sample size of only eight patients on topsalysin and two patients on vehicle in each cohort was insufficient to show statistically significant improvements in BPH symptoms compared to vehicle. Although improvement in IPSS was noted on average for all dose cohorts through 12 months, there is no meaningful difference between topsalysin and vehicle-treated patients. We do not believe that any conclusions about efficacy can be drawn from this study due to the small sample size.

In our TRIUMPH clinical trial, we observed post-injection transient elevations of two markers: PSA, a marker of prostate tissue disruption, and serum C-reactive protein, or CRP, a non-specific marker of associated inflammation. Post-injection transient elevations in PSA and CRP were also observed in the transrectal study, suggesting that the targeted delivery of topsalysin to the prostate is successfully achieved with either the transperineal or the transrectal route of administration.

Phase 2a Open-Label Clinical Trial in BPH (PRX302-2-02)

In 2009, we completed an open-label, multicenter, Phase 2a clinical trial in BPH to evaluate the safety and tolerability of topsalysin. We enrolled 18 patients with moderate to severe BPH symptoms who were either unresponsive to, intolerant to or unwilling to use oral medications for treatment of the symptoms of BPH. In this clinical trial, three cohorts of six patients each received a single treatment of topsalysin administered via transperineal injection. We measured therapeutic activity through changes in IPSS, Qmax, and quality of life scores compared to baseline scores at screening. In addition, we monitored changes in prostate volume. In this clinical trial, topsalysin was well-tolerated and patients attained meaningful symptomatic relief through follow up of 12 months following a single treatment. Based on the results of this clinical trial, we identified 20% of total prostate volume as our volume dose for our Phase 2b clinical trial.

Phase 1 Open-Label Clinical Trial in BPH (PRX302-2-01)

In 2008, we completed an open-label, multicenter, Phase 1 clinical trial in BPH to evaluate the dose of topsalysin needed to demonstrate therapeutic activity following a single treatment, as well as to evaluate safety and tolerability. We enrolled 15 patients with moderate to severe BPH symptoms who were either unresponsive to, intolerant to or unwilling to use oral medications for treatment of the symptoms of BPH. We administered topsalysin to five cohorts of three patients each at escalating doses of topsalysin. Topsalysin was well-tolerated.

Plans for Future Clinical Development in BPH

In order to seek regulatory approval for topsalysin for the treatment of the symptoms of BPH, we will be required to successfully conduct a second Phase 3 clinical trial.

We are currently not planning on pursuing a second Phase 3 trial in BPH, unless we secure a development partner to fund such new clinical trial or obtain other financing. There can be no assurance that such funding or a development partner will be available on acceptable terms or at all. For that reason, we cannot currently estimate when the clinical development required to seek the regulatory approvals needed to commercialize topsalysin for the treatment of the symptoms of BPH will be completed.

To date, no BPH patients have been administered more than one treatment of topsalysin. Assuming sufficient capital resources, we would plan to initiate an open label repeat dose clinical trial in which patients from our transrectal clinical trial, as well as patients from our first Phase 3 clinical trial, will be eligible to receive a repeat dose of topsalysin, at least 12 months after their first dose. We believe this repeat dose Phase 3 clinical trial is supported by results from our pre-clinical study of repeat dosing in monkeys. In this pre-clinical study, two treatments of topsalysin were given to monkeys 56 days apart. Data from this study indicated that topsalysin resulted in ablation of cells after both the first and the second dose, even in the presence of circulating antibodies, and did not result in hypersensitivity.

Competition

In the treatment of clinically significant localized prostate cancer we expect that topsalysin will compete with radical treatments such as prostatectomy and radiation as well as a number of other targeted focal therapies which are gaining traction such as brachytherapy, high-intensity focused ultrasound, cryotherapy, laser ablation, radiofrequency ablation and photodynamic therapy (padeliporfin di-potassium).

The increasing use of mpMRI of the prostate and advances in software to co-register previously obtained mpMRI images with live 3D ultrasound images enables physicians to more accurately target their prostate biopsies. Consequently, it is increasingly possible to more confidently identify men with clinically significant lesions. Thereby, enabling physicians and patients to make a more informed decision about the clinical significance of their disease and whether their disease requires a radical treatment approach with the potential for significant morbidity or whether they may be a candidate for targeted focal therapy where the objective is to remove the significant disease while preserving the as much of the prostate as possible and potentially avoiding many of the complications and side effects associated with the radical whole gland treatments.

In 2017, padeliporfin was approved by the EMA for the treatment of low risk prostate cancer which is defined as prostate cancer with a Gleason score equal to or less than 6 and a maximum cancer core length of less than 5 millimeters. In January 2018, Nymox Pharmaceuticals, or Nymox, announced top-line five year clinical trial biopsy data from the intraprostatic administration of its investigational therapy NX-1207 (fexapotide triflutate) in patients with low grade localized (T1c) prostate cancer.

We expect that topsalysin will compete with the current treatment options for the symptoms of BPH, which include oral drug therapy and surgery. Oral drug therapies include alpha-blockers, such as tamsulosin (marketed under various trade names by numerous companies, including as Flomax® by Astellas Pharma), alfuzosin (marketed in the United States by Sanofi as Uroxatral®), doxazosin (marketed by Pfizer as Cardura® and CarduraXL®) and silodosin (marketed by Watson Pharmaceuticals as Rapaflo® in the United States), (b) 5-alpha reductase inhibitors, such as dutasteride (marketed by GlaxoSmithKline plc as Avodart®) and finasteride (marketed by Merck & Co., Inc. as Proscar®), and (c) combinations of a-blockers and 5-alpha reductase inhibitors such as tamsulosin and dutasteride (marketed by GSK as Jalyn®). In addition, Eli Lilly and Company's oral drug tadalafil (marketed as Cialis®), a PDE5 inhibitor, obtained FDA approval for the treatment of the symptoms of BPH in October 2011. Several MIST procedures are available, including transurethral microwave thermotherapy, or TUMT, TUNA, photo-selective vaporization of prostate, holmium laser enucleation of the prostate, transurethral electro vaporization of the prostate, Urolift, which is designed to open the urethra directly without the need to resect or ablate prostate tissue and interstitial laser coagulation. A new TUNA, Rezum by NxThera which delivers radiofrequency generated thermal therapy in the form of water vapor via a transurethral needle, received approval in September 2015 and became available on the US markets late 2016. Currently, the most commonly used MIST procedures are laser ablations of the prostate, TUMT, and TUNA. Surgery for BPH treatment is usually considered in patients who fail drug therapy as a result of side effects or inadequate relief of symptoms, have refractory urinary retention, or have recurrent urinary tract infections. Alternatively, surgery may be the initial treatment in patients with severe urinary symptoms. Surgical procedures for BPH include TURP, as well as other procedures such as transurethral incision of the prostate and transurethral vaporization of the prostate.

In addition, there are other treatments that are currently in clinical development for the treatment of the symptoms of BPH. In late 2016, Procept BioRobotics announced the completion of enrollment with 184 patients in a global Phase 3 clinical trial to evaluate the AquaBeam System, a waterjet ablation therapy for endoscopic resection of prostate tissue. Light Sciences Oncology Inc.'s Aptocine™ is currently in Phase 2 clinical trials. Nymox has announced that it plans to submit a New Drug Application for Fexapotide Triflutate for the treatment of BPH in the United States.

Sales and Marketing

We do not currently have a sales, marketing or distribution organization. We intend to commercialize topsalysin by establishing, either internally or through a contract sales force, a urology sales force to sell topsalysin, if approved, in the United States, or through partnership. We plan to partner with third parties to commercialize topsalysin outside the United States.

Specifically, we intend to:

- establish a sales force in the United States of experienced urology and other specialty-care sales representatives;
- build a marketing organization;
- establish commercialization alliances with larger or more specialized pharmaceutical and sales organizations; and
- generate and use pharmacoeconomic data to support the cost savings and therapeutic benefits of topsalysin.

Manufacturing

We neither currently possess nor do we plan to develop our own manufacturing capabilities. All of our manufacturing is, and will be, outsourced to third parties with oversight by our internal managers. In 2012, we entered into a manufacturing and supply agreement with Boehringer Ingelheim RCV GmbH & Co KG, or BI, to manufacture topsalysin. The manufacture of topsalysin drug substance starts with a vial of the working cell bank of *Aeromonas salmonicida* bacteria which is then processed through four consecutive stages involving: batch fermentation and harvest, purification using immobilized metal affinity chromatography, purification using an ionic exchange chromatography and bulk formulation of topsalysin drug substance. The entire manufacturing process takes approximately two weeks. There has been a successful scale-up up to the commercial batch size for drug substance. We recently completed the successful manufacture of a batch of drug substance which provided sufficient clinical material to complete a potential registration study for the treatment of localized prostate cancer.

The finalization of the commercial fill finish process, for the production of drug product is still underway but we have recently completed a project which optimized our current drug product formulation for topsalysin. We have selected Vetter Pharma International GmBH, or Vetter, to work on the completion of the specifications for the fill finish process for the production of reformulated topsalysin drug product and to supply clinical trial drug product material. We are currently in the process of negotiating a long-term contract with Vetter. Vetter has recently completed a successful engineering campaign and we expect Vetter to complete a GMP fill finish of our new drug product formulation before the end of the first half of 2019. We expect that this fill finish campaign will provide sufficient clinical material for us to complete a potential registration study for the treatment of localized prostate cancer. Although topsalysin is manufactured from readily available materials using standard pharmaceutical methods and equipment, the process of transferring the technology to manufacture our new drug product may lead to significant delays and increase our costs. We will also need to demonstrate that our new drug product formulation is comparable to our prior drug product formulation. Any delay in the technology transfer to Vetter or completion of fill finish for our future clinical trial supply would result in future delays in our ability to commence additional clinical trials.

Our prior drug product formulation required that we procured an ingredient from a multinational industrial biotech company which was a single source supplier. Our new drug product formulation does not use this sole sourced ingredient.

Supply Agreement with Boehringer Ingelheim RCV GmbH & Co KG

In June 2012, we entered into a technology transfer and supply agreement with BI, for the provision of technology transfer services and for the establishment of certain manufacturing processes for, and the manufacture of, purified topsalysin, the diluting agent for use in topsalysin drug products and placebos, and a placebo to be used in clinical trials. We will be required to make payments based upon the provision and completion of certain tasks specified in the agreement. Starting in 2013, the prices of BI's services have been adjusted annually based on the average of the Austrian trade index and the average Standard Wages Index, both as of July of the previous year, subject to certain restrictions. BI will be required to manufacture the products in line with certain project timelines. If we postpone the performance of any services, we may be required to pay certain postponement fees. Additionally, if we cancel any services we will be required to pay the entire cost for such services and the entire cost of any materials that cannot be returned by BI to the appropriate vendor or otherwise used by BI. If we are required to have any product manufactured outside our expected manufacturing cycles due to an unforeseen loss of product, we will have to work with BI to arrange an available manufacturing slot and our receipt of drug product may be delayed. BI must provide all services under the agreement, including the manufacture, packaging, storing and delivery of topsalysin drug products, in accordance with cGMP (as defined below), as specified by the FDA. The agreement has an initial term of six years and will automatically renew for a single five-year period unless either party objects to such renewal at least two-years prior to the expiration of the agreement. Either party may terminate the agreement early for cause, including for any uncured material breach of the agreement, the other party's insolvency or the assignment of the other party's rights or obligations to a direct competitor of the non-assigning party. Additionally, we have the right to terminate the agreement immediately upon the rejection or non-approval of a regulatory filing due to medical, safety or regulatory concerns or in the event that we abandon our clinical program for topsalysin due to any clinical failure, subject in each case to payment of specified termination costs to BI.

Intellectual Property

We hold commercial rights to topsalysin in major markets, including, Canada, the United States, Europe and Asia (except Japan where we have licensed the rights to Kissei). We in-licensed topsalysin from UVIC and Johns Hopkins. Our success will depend in large part on our ability to obtain, maintain, defend and enforce patents and other proprietary technology rights. We file and prosecute patent applications to protect our proprietary discoveries. In addition to patent protection, we also seek to rely on trade secret protection, trademark protection and know-how to expand our proprietary position around our technology, discoveries and inventions that we consider important to our business. We also seek to protect our intellectual property in part by entering into confidentiality agreements and/or invention assignment agreements with our employees, consultants, scientific advisors, and certain consultants and investigators that grant us ownership of any discoveries or inventions made by them. Further, we seek trademark protection in Canada, the United States and certain other countries where available and when we deem appropriate. We have registered the Sophiris trademark, which we use in connection with our pharmaceutical research and development services as well as our clinical-stage product candidates in Europe, Canada, Japan and the United States.

Patents and patent applications covering topsalysin which we license or own are covered by issued patents and patent applications under the following five patent families:

- Proaerolysin Containing Protease Activation Sequences and Methods of Use for Treatment of Prostate Cancer (exclusively licensed);
- Method of Treating or Preventing Benign Prostatic Hyperplasia (BPH) Using Modified Pore-Forming Proteins (exclusively licensed);
- Method for Treating Prostatitis Utilizing Modified Pore-Forming Protein Proaerolysin (exclusively licensed);
- Targeted Focal Treatment for Localized Prostate Cancer (owned by us); and
- Methods of Treatment of Prostate Cancer and Lower Urinary Tract Symptoms (owned by us).

We own or have exclusively licensed seven issued United States patents related to our prostate program: US 7,282,476 (prostate cancer) expiring in 2023, US 7,745,395 (prostate cancer) expiring in 2023, US 7,838,266 (prostate cancer) expiring in 2022, US 8,278,279 (prostatitis) expiring in 2029, US 8,901,070 (prostatitis) expiring in 2029, US 8,916,161 (BPH) expiring in 2031, and US 9,950,029 (BPH) expiring in 2031, as well as nine issued patents in countries including Australia, China, the European Patent Office (including 16 validation states), Canada, India, Japan, Hong Kong, and South Africa expiring in 2022, ten patents in the European Patent Office (including 13 validation states), Canada, Japan, Korea, China, Australia, New Zealand, Israel, Singapore, and South Africa expiring in 2026, and additional pending U.S. and/or foreign patent applications in Australia, Canada, China, the European Patent Office, and Japan, variously set to expire in 2029 or 2037. This portfolio includes issued United States patents that cover the composition of topsalysin and methods of using topsalysin to treat prostatitis, prostate cancer, and symptoms of BPH. This portfolio includes two issued Chinese patents. To date, we have not sought to enforce any issued patents in China. We cannot give any assurances that we will be able to enforce our patents in China to the same degree that we could in the United States.

Technology Licenses

Exclusive License Agreement with UVIC Industry Partnerships Inc. and The Johns Hopkins University for Prostate Cancer

In September 2004, we entered into an exclusive license agreement with UVIC and Johns Hopkins, with respect to the use of topsalysin for the development of therapeutics for prostate cancer. This agreement was amended on December 8, 2004 and July 1, 2010. Such amendments did not change the material terms of the agreement. For the term of this agreement, we have an exclusive right of first option to obtain a license for future improvements to the patent rights covered by the agreement. In addition, we have the right to grant sublicenses to third parties under the agreement provided that such sublicenses meet certain criteria.

In order to secure the license, we paid an initial license fee of CND$75,000, or $62,000, applying the conversion rate as of the date of payment, and a reimbursement fee of CND$28,000, or $24,000, applying the conversion rate as of the date of payment, to cover expenses associated with the filing and maintenance fees of patents covered by the agreement. In addition, we are required to pay an annual license maintenance fee and are obligated to pay a percentage of gross sales for licensed products sold by us, our affiliates or our sublicensees during the term of the agreement. Such percentage is in the low single-digits and is subject to adjustment in certain circumstances. We are also required to make payments based upon the achievement of specific development and regulatory milestones totaling up to approximately CND$3.6 million, or $2.6 million, as converted.

In the event we receive consideration for granting a sublicense, we are obligated to pay UVIC and Johns Hopkins a percentage of such consideration, which percentage is in the 20-29% range, including any future consideration we may receive under our exclusive license agreement with Kissei relating to development of therapeutics for the treatment of prostate cancer however, pursuant to a separate agreement which we entered into in 2003 with Dr. J. Thomas Buckley, one of our founders, the aggregate amount of such consideration payable by us to UVIC and Johns Hopkins was reduced by 25%. Furthermore, we issued 3,420 common shares to Johns Hopkins and 1,710 common shares to UVIC in partial consideration for the rights granted to us under the agreement.

Under the terms of the agreement, we are required to use reasonable commercial efforts to develop and commercialize the technology covered by the agreement, and in this regard, have agreed to put a business plan in place. Our failure to commercialize the technology covered by the agreement may result in termination of the agreement.

The term of the agreement will, on a country-by-country basis, continue until expiration of the last to expire issued patent or, if no patent has issued in such country, then 20 years after the effective date of the agreement.

UVIC and Johns Hopkins have a unilateral right to terminate the agreement upon notice if we become insolvent, cease to carry out our business, subject the licensed technology to any security interest or breach any of our obligations under this agreement if such breach has remained uncured for 60 days following written notice thereof. In addition, the agreement may automatically terminate in the event we undergo bankruptcy proceedings.

Exclusive License Agreement with UVIC Industry Partnerships Inc. and The Johns Hopkins University for BPH

In October 2009, we entered into an exclusive license agreement with UVIC and Johns Hopkins with respect to the use of topsalysin for the development of therapeutics for the symptoms of BPH and other non-cancer diseases and conditions of the prostate, as amended in July 2010. Such amendment did not change the material terms of the agreement. We have the right to grant sublicenses to third parties under the agreement provided that such sublicenses meet certain criteria.

In order to secure the license, we paid an initial license fee of CND$45,000, or $39,000, applying the conversion rate as of the date of payment. In addition, we are required to pay an annual license maintenance fee and are obligated to pay a percentage of gross sales for licensed products sold by us, our affiliates or our sublicensees during the term of the agreement. Such percentage is in the low single-digits. Furthermore, we are required to make payments based upon the achievement of specific development and regulatory milestones separated among the indications of BPH and two additional therapeutic indications selected by us, totaling up to approximately CND$1.3 million, or $1.0 million, as converted. In the event we receive consideration for granting a sublicense, we are obligated to pay UVIC and Johns Hopkins a percentage of such consideration, which percentage is in the 10-19% range, depending upon the rights granted under the sublicense agreement. To the extent we receive any milestone payments relating to the development of therapeutics for the treatment of the symptoms of BPH under our exclusive license agreement with Kissei we are obligated to pay a percentage of such consideration, which percentage is in the 10-19% range, to UVIC and Johns Hopkins; however, pursuant to a separate agreement which we entered into in 2003 with Dr. J. Thomas Buckley, one of our founders, the aggregate amount of such consideration payable by us to UVIC and Johns Hopkins was reduced by 25%.

Under the terms of the agreement, we are required to use reasonable commercial efforts to develop and commercialize the technology covered by the agreement, and in this regard, we have agreed to put a business plan covering the marketing and commercialization of such technology in place. Our failure to commercialize the technology covered by the agreement may result in termination of the agreement.

The term of the agreement will, on a country-by-country basis, continue until expiration of the last to expire issued patent or, if no patent has issued in such country, then 20 years after the effective date of the agreement. UVIC and Johns Hopkins have a unilateral right to terminate the agreement upon notice if we become insolvent, cease to carry out our business, subject the licensed technology to any third-party security interest or breach any of our obligations under this agreement if such breach has remained uncured for 60 days following written notice thereof. In addition, the agreement may automatically terminate in the event we undergo bankruptcy proceedings.

Strategic Relationship with Kissei Pharmaceutical Co., Ltd.

In April 2010, we entered into an exclusive license agreement with Kissei, for the development and commercialization of topsalysin (and other products covered by the licensed patents) in Japan for the treatment of the symptoms of BPH, prostate cancer, prostatitis or other diseases of the prostate. Under the terms of the license, Kissei is permitted to sublicense its rights if certain conditions are met.

In order to secure the license, Kissei paid us an up-front payment of $3.0 million. During the year ended December 31, 2013, we recorded as revenue a $5.0 million non-refundable milestone payment due from Kissei upon the achievement of certain development activities. In addition, we remain eligible to receive up to approximately $67.0 million in additional payments contingent upon achievement of specified development, regulatory and commercial milestones, some of which are in Kissei's sole discretion to achieve, separated among the indications of BPH, prostate cancer, and prostatitis or other diseases of the prostate, as well as the achievement of overall accumulated gross sales levels for such indications. The additional $67.0 million of non-refundable milestone payments is comprised as follows: aggregate milestone payments of $12.0 million are related to the BPH indication, of which $7.0 million relates to the completion of regulatory approvals and $5.0 million relates to the achievement of certain product sale goals; a total of $21.0 million is related to the prostate cancer indication, of which $7.0 million relates to the completion of development activities, $7.0 million relates to the completion of regulatory approvals and $7.0 million relates to the achievement of certain product sale goals; and a total of $21.0 million is related to prostatitis or other diseases of the prostate, of which $7.0 million relates to the completion of development activities, $7.0 million relates to the completion of regulatory approvals and $7.0 million relates to the achievement of certain product sale goals. An additional $13.0 million of aggregate milestone payments are not indication specific, of which $5.0 million relates to the completion of regulatory approvals and $8.0 million relates to the achievement of certain product sale goals. In addition, we may receive a drug supply fee and royalty payments in the 20-29% range as a percentage of future net sales of licensed products sold under the agreement. The royalties payable by Kissei are subject to reductions or offsets in certain circumstances. Kissei's royalty obligations continue until the later of expiration of the last valid claim in the licensed patents covering the applicable licensed product, or 10 years after first commercial sale of such licensed product in Japan. Kissei is responsible for all costs associated with the development, regulatory approval, commercialization and marketing of topsalysin in Japan.

Kissei may unilaterally terminate the agreement, provided that if such termination occurs after commercial launch of a product under the agreement, Kissei must provide us with six months prior written notice. Absent early termination, the exclusive license agreement will remain in effect until Kissei or its sublicensees or affiliates discontinue the sale of products under the agreement.

Regulatory Overview

Our business and operations are subject to a variety of U.S. federal, state and local, and foreign supranational, national, provincial and municipal laws, regulations and trade practices. The FDA and comparable regulatory authorities in state and local jurisdictions and in other countries impose substantial and burdensome requirements upon companies involved in the clinical development, manufacture, marketing and distribution of drugs and biologics. These agencies and other federal, state and local entities regulate research and development activities and the testing, manufacture, quality control, safety, effectiveness, labeling, storage, recordkeeping, approval, advertising and promotion, and export and import of our product candidate.

U.S. Government Regulation

U.S. Drug Development Process

In the United States, the FDA regulates drugs and biologic products under the Federal Food, Drug and Cosmetic Act, or FDCA, its implementing regulations, and other laws, including, in the case of biologics, the Public Health Service Act. Our product candidate, topsalysin, is subject to regulation by the FDA as a biologic. Biologics require the submission of a BLA to the FDA and approval of the BLA by the FDA before marketing in the United States. The process of obtaining regulatory approvals for commercial sale and distribution and the subsequent compliance with applicable federal, state, local and foreign statutes and regulations require the expenditure of substantial time and financial resources. 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 to administrative or judicial civil or criminal sanctions. These sanctions could include the FDA's refusal to approve pending applications, license suspension or revocation, withdrawal of an approval, imposition of a clinical hold on clinical trials, warning letters, product recalls, product seizures, total or partial suspension of production or distribution, injunctions, fines, refusals of government contracts, restitution, disgorgement or civil and/or criminal penalties. The process required by the FDA before a biologic may be marketed in the United States generally involves the following:

- completion of preclinical laboratory tests, animal studies and formulation studies performed in accordance with the FDA's current Good Laboratory Practices, or GLP, regulations;
- submission to the FDA of an investigational new drug application, or IND, which must become effective before human clinical trials in the United States may begin;
- performance of adequate and well-controlled human clinical trials in accordance with the FDA's current good clinical practices, or GCP, regulations to establish the safety and efficacy of the product candidate for its intended use;
- submission to the FDA of a BLA;
- satisfactory completion of an FDA inspection of the manufacturing facility or facilities where the product is produced to assess compliance with the FDA's current good manufacturing practice standards, or cGMP, regulations to assure that the facilities, methods and controls are adequate to preserve the product's identity, strength, quality and purity;
- potential audits by the FDA of the nonclinical and clinical trial sites that generated the data in support of the BLA;
- possible review of the BLA by an external Advisory Committee to the FDA, whose recommendations are not binding on the FDA; and
- FDA review and approval of the BLA prior to any commercial marketing or sale.

Before testing any compounds with potential therapeutic value in humans, the drug candidate enters the preclinical testing stage. Preclinical tests include laboratory evaluations of product chemistry, stability and formulation, as well as animal studies to assess the potential toxicity and activity of the product candidate. The conduct of the preclinical tests must comply with federal regulations and requirements including GLPs. The 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. The IND automatically becomes effective 30 days after receipt by the FDA, unless the FDA raises concerns or questions about the conduct of the clinical trial, including concerns that human research subjects will be exposed to unreasonable health risks. 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, or for other reasons.

Clinical trials involve the administration of the product candidate to human subjects 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, subject selection and exclusion criteria, and the parameters to be used to monitor subject safety and effectiveness. Each protocol must be submitted to the FDA as part of the IND. Clinical trials must be conducted in accordance with GCPs. Further, each clinical trial must be reviewed and approved by an 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 that must be signed by each clinical trial subject or his or her legal representative and must monitor the clinical trial until completed. Human clinical trials are typically conducted in three sequential phases that may overlap or be combined:

- *Phase 1*. The product candidate is initially introduced into a limited population of healthy human subjects and tested for safety, dosage tolerance, absorption, metabolism, distribution and excretion. In the case of some products for some diseases, or when the product may be too inherently toxic to ethically administer to healthy volunteers, the initial human testing is often conducted in patients with the disease or condition for which the product candidate is intended to gain an early indication of its effectiveness.

- *Phase 2*. The product candidate is evaluated in a limited patient population (but larger than in Phase 1) to identify possible adverse effects and safety risks, to preliminarily evaluate the efficacy of the product for specific targeted indications and to assess dosage tolerance, optimal dosage and dosing schedule.

- *Phase 3*. Clinical trials are undertaken to further evaluate dosage and provide substantial evidence of clinical efficacy and safety in an expanded patient population (such as several hundred to several thousand) at geographically dispersed clinical trial sites. Phase 3 clinical trials are typically conducted when Phase 2 clinical trials demonstrate that a dose range of the product candidate is effective and has an acceptable safety profile. These trials typically have at least two groups of patients who, in a blinded fashion, receive either the product or a placebo. Phase 3 clinical trials are intended to establish the overall risk/benefit ratio of the product and provide an adequate basis for product labeling. Generally, two adequate and well-controlled Phase 3 clinical trials are required by the FDA for approval of a BLA.

Post-approval studies, sometimes referred to as Phase 4 clinical trials, may be conducted after initial marketing approval. These studies are used to gain additional experience from the treatment of patients in the intended therapeutic indication to further assess the biologic's safety and effectiveness after BLA approval. Phase 4 studies can be initiated by the drug sponsor or as a condition of BLA approval by the FDA.

Annual progress reports detailing the results of the clinical trials must be submitted to the FDA and written IND safety reports must be promptly submitted to the FDA and the investigators for serious and unexpected adverse events or any finding from tests in laboratory animals that suggests a significant risk for human subjects.

Concurrent with clinical trials, companies usually complete additional animal studies and must also develop additional information about the chemistry and physical characteristics of the biologic and finalize a process for manufacturing the product in commercial quantities in accordance with cGMP requirements. The manufacturing process must be capable of consistently producing quality batches of the product candidate and, among other things, must develop methods for testing the identity, strength, quality and purity of the final biologic product. Additionally, appropriate packaging must be selected and tested and stability studies must be conducted to demonstrate that the product candidate does not undergo unacceptable deterioration over its shelf life.

U.S. Review and Approval Processes

The results of product development, preclinical studies and clinical trials, along with descriptions of the manufacturing process, analytical tests, proposed labeling and other relevant information are submitted to the FDA in the form of a BLA requesting approval to market the product for one or more specified indications. The submission of a BLA is subject to the payment of substantial user fees.

Once the FDA receives a BLA, it has 60 days to review the BLA to determine if it is substantially complete and the data is readable, before it accepts the BLA for filing. Once the submission is accepted for filing, the FDA begins an in-depth review of the BLA. Under the goals and policies agreed to by the FDA under the Prescription Drug User Fee Act, or PDUFA, the FDA has 12 months from submission in which to complete its initial review of a standard BLA and make a decision on the application, and eight months from submission for a priority BLA, and such goal is referred to as the PDUFA date. The FDA does not always meet its PDUFA dates for either standard or priority BLAs. The review process and the PDUFA date may be extended by three months if the FDA requests or the BLA sponsor otherwise provides additional information or clarification regarding information already provided in the submission within the last three months before the PDUFA date.

After the BLA submission is accepted for filing, the FDA reviews the BLA to determine, among other things, whether the proposed product is safe and effective for its intended use, and whether the product is being manufactured in accordance with cGMP to assure and preserve the product's identity, strength, quality and purity. The FDA may refer applications for novel drug or biological products or drug or biological products which 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 approval process, the FDA also will determine whether a risk evaluation and mitigation strategy, or REMS, is necessary to assure the safe use of the product. If the FDA concludes a REMS is needed, the sponsor of the BLA must submit a proposed REMS; the FDA will not approve the BLA without an approved REMS, if required. Development of a REMS can substantially increase the costs of obtaining approval.

Before approving a BLA, the FDA will typically inspect the facilities at which the product is manufactured. The FDA will not approve the BLA unless it determines that the manufacturing processes and facilities are in 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 studies were conducted in compliance with GCP requirements. If the FDA determines that the application, manufacturing process or manufacturing facilities are not acceptable, it will outline the deficiencies in the submission and often will request additional testing or information before a BLA can be approved.

The FDA will issue a complete response letter if the agency decides not to approve the BLA. The complete response letter 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 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. In addition, the FDA may require post marketing studies, sometimes referred to as Phase 4 testing, which involves clinical trials designed to further assess drug safety and effectiveness and may require testing and surveillance programs to monitor the safety of approved products that have been commercialized. After approval, certain changes to the approved biologic, such as adding new indications, manufacturing changes or additional labeling claims, are subject to further FDA review and approval. Depending on the nature of the change proposed, a BLA supplement must be filed and approved before the change may be implemented. For many proposed post-approval changes to a BLA, the FDA has up to 180 days to review the application. As with new BLAs, the review process is often significantly extended by the FDA requests for additional information or clarification.

Post-Approval Requirements

Any biologic products for which we or our collaborators receive FDA approvals are subject to continuing regulation by the FDA, including, among other things, record-keeping requirements, reporting of adverse experiences with the product, providing the FDA with updated safety and efficacy information, product sampling and distribution requirements, complying with certain electronic records and signature requirements and complying with FDA promotion and advertising requirements, which include, among others, restrictions on direct-to-consumer advertising, promoting biologics 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. The FDA closely regulates the post-approval marketing and promotion of biologics, and although physicians may prescribe legally available drugs for off-label uses, manufacturers may not market or promote such off-label uses. However, companies may share truthful and not misleading information that is otherwise consistent with the product's FDA approved labeling. Failure to comply with these or other FDA requirements can subject a manufacturer to possible legal or regulatory action, such as warning letters, suspension of manufacturing, seizure of product, injunctive action, mandated corrective advertising or communications with healthcare professionals, possible civil or criminal penalties, or other negative consequences, including adverse publicity.

We will rely, and expect to continue to rely, on third parties for the production of clinical and commercial quantities of our products. Our collaborators may also utilize third parties for some or all of a product we are developing with such collaborator. Manufacturers are required to comply with applicable FDA manufacturing requirements contained in the FDA's cGMP regulations. cGMP regulations require among other things, quality control and quality assurance as well as the corresponding maintenance of records and documentation. Drug manufacturers and other entities involved in the manufacture and distribution of approved biologics are required to register their establishments with the FDA and certain state agencies and are subject to periodic inspections by the FDA and certain state agencies for compliance with cGMP 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.

U.S. Patent Term Restoration and Marketing Exclusivity

Depending upon the timing, duration and specifics of the FDA approval of our biologic product candidate, some of our United States 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 product is eligible for the extension and the application for the extension must be submitted prior to the expiration of the patent. The United States 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.

Market exclusivity provisions under the FDCA can also delay the submission or the approval of certain applications of other companies seeking to reference another company's BLA. We believe that if topsalysin is approved as a biological product under a BLA, it should qualify for a 12-year period of exclusivity currently permitted by the Biologics Price Competition and Innovation Act of 2009, or BPCIA. Under the BPCIA, an application for a biosimilar product cannot be approved by the FDA until 12 years after the original branded product was approved under a BLA. However, an application may be submitted after four years if it contains a certification of patent invalidity or non-infringement to one of the patents listed with the FDA by the innovator BLA holder. The BPCIA is complex and is only beginning to be interpreted and implemented by the FDA.

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 otherwise influence a person working in an official capacity.

U.S. Federal and State Health Regulation Laws

In addition to FDA restrictions on marketing of pharmaceutical products, several other types of state and federal laws have been applied to restrict certain marketing practices in the biopharmaceutical industry in recent years. These laws include anti-kickback statutes, false claims statutes, patient data privacy and security laws, and physician sunshine laws and regulations, many of which may become more applicable if our product candidates are approved and we begin commercialization.

The federal health care program anti-kickback statute prohibits, among other things, knowingly and willfully offering, paying, soliciting, or receiving remuneration to induce or in return for purchasing, leasing, ordering, or arranging for the purchase, lease, or order of any health care item or service reimbursable 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, and formulary managers on the other. Although there are a number of statutory exceptions and regulatory safe harbors protecting certain common activities from prosecution, the exceptions and safe harbors are drawn narrowly, and practices that involve remuneration intended to induce prescribing, purchases, or recommendations may be subject to scrutiny if they do not satisfy the requirements of an exception or safe harbor. Our practices may not in all cases meet all of the criteria for safe harbor protection from anti-kickback liability.

Federal false claims laws and civil monetary penalties laws prohibit, among other things, any person or entity from knowingly presenting, or causing to be presented, a false claim for payment to the federal government, or knowingly making, or causing to be made, a false statement to get a false claim paid. The majority of states also have statutes or regulations similar to the federal anti-kickback law 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, including commercial payors.

The federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, created additional federal civil and criminal statutes that prohibit, among other things, executing a scheme to defraud any healthcare benefit program and making false statements relating to healthcare matters. HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act, or HITECH, and their implementing regulations, also imposes certain requirements relating to the privacy, security and transmission of individually identifiable health information. We are also subject to state 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.

The Physician Payments Sunshine Act, and its implementing regulations, require 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) to report annually information related to certain payments or other transfers of value made or distributed to physicians and teaching hospitals, or to entities or individuals at the request of, or designated on behalf of, physicians and teaching hospitals and to report annually certain ownership and investment interests held by physicians and their immediate family members. Additional state laws require pharmaceutical companies to implement a comprehensive compliance program and/or limit expenditure for, or payments to, individual medical or health professionals, and require the reporting of information relating to drug pricing. Certain state and local laws also require the registration of pharmaceutical sales representatives.

Because of the breadth of these laws and the narrowness of the applicable 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. If our operations are found to be in violation of any of the health regulatory laws described above or any other laws that apply to us, we may be subject to penalties, including potentially significant criminal, civil and administrative penalties, damages, fines, disgorgement, imprisonment, exclusion from participation in government healthcare programs, contractual damages, reputational harm, administrative burdens, integrity oversight and reporting obligations, diminished profits and future earnings, and the curtailment or restructuring of our operations, any of which could adversely affect our ability to operate our business and our results of operations.

In the United States and foreign jurisdictions, there have been and continue to be a number of initiatives that seek to promote changes in healthcare systems with the stated goals of containing healthcare costs, improving quality and/or expanding access. For example, in March 2010 the Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act, or collectively the PPACA, was enacted, which included measures to significantly change the way health care is financed by both governmental and private insurers. Among the provisions of the PPACA of greatest importance to the pharmaceutical and biotechnology industry are that it:

- created an annual, nondeductible fee on any entity that manufactures or imports certain branded prescription drugs and biologic agents, apportioned among these entities according to their market share in certain government healthcare programs;
- created new requirements on certain manufacturers of drugs, devices, biological products and medical supplies to report annually certain financial arrangements, including reporting any "transfer of value" made or distributed to physicians and teaching hospitals and reporting annually certain ownership and investment interests held by physicians and their immediate family members;
- created a new requirement to annually report drug samples that certain manufacturers and authorized distributors provide to physicians;
- created a new Patient-Centered Outcomes Research Institute to oversee, identify priorities in, and conduct comparative clinical effectiveness research, along with funding for such research;
- created a licensure framework for follow-on biological products;
- increased the statutory minimum rebates a manufacturer must pay under the Medicaid Drug Rebate Program, extended manufacturers' Medicaid rebate liability, expanded the eligibility criteria for people to participate in the Medicaid program, and created a new Medicare Part D coverage gap discount program; and
- established a Center for Medicare & Medicaid Innovation at the Centers for Medicare & Medicaid Services, or CMS, to test innovative payment and service delivery models to lower Medicare and Medicaid spending, potentially including prescription drug spending.

Since its enactment there have been judicial and Congressional challenges to certain aspects of the PPACA, and we expect there will be additional challenges and amendments to the PPACA in the future. On December 14, 2018, a Texas U.S. District Court Judge ruled that PPACA is unconstitutional in its entirety because the "individual mandate" was repealed by Congress as part of the Tax Cuts and Jobs Act of 2017. 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 PPACA will impact the PPACA.

In addition, other legislative changes have been proposed and adopted since the PPACA was enacted. For example, in August 2011, the President signed into law the Budget Control Act of 2011, which, among other things, created the Joint Select Committee on Deficit Reduction to recommend to Congress proposals in spending reductions. The Joint Select Committee did not achieve a targeted deficit reduction of at least $1.2 trillion for the years 2013 through 2021, triggering the legislation's automatic reduction to several government programs. This included reductions to Medicare payments to providers of 2% per fiscal year, which went into effect in April 2013 and, following passage of the Bipartisan Budget Act of 2015, as well as other legislative amendments to the statute, will stay in effect through 2027 unless additional Congressional action is taken. Additionally, in January 2013, the American Taxpayer Relief Act of 2012 was signed into law, which, among other things, reduced Medicare payments to several providers, including hospitals and imaging centers. Further, recently there has been heightened governmental scrutiny over the manner in which manufacturers set prices for their marketed products. For example, there have been several recent U.S. Congressional inquiries and proposed and enacted federal and state legislation designed to, among other things, bring more transparency to drug pricing, review the relationship between pricing and manufacturer patient programs, and reform government program reimbursement methodologies for drugs. For example, 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. On January 31, 2019, the U.S. Department of Health and Human Services, Office of Inspector General, proposed modifications to the federal health care program anti-kickback statute discount safe harbor for the purpose of reducing the cost of drug products to consumers which, among other things, if finalized, will affect discounts paid by manufacturers to Medicare Part D plans, Medicaid managed care organizations and pharmacy benefit managers working with these organizations. While some of these and other proposed measures may 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.

We expect that additional federal and state healthcare reform measures will be adopted in the future, any of which could result in reduced demand for our products or other adverse effects.

Europe / Rest of World Government Regulation

In addition to regulations in the United States, we, and our collaborators, 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. For example, the European Union, or EU, has established its own data security and privacy legal framework, including but not limited to Directive 95/46/EC, or the Data Protection Directive. The recently adopted European General Data Protection Regulation, or GDPR, contains new provisions specifically directed at the processing of health information, higher sanctions and extra-territoriality measures that are intended to bring non-EU companies under the data security and privacy legal framework specified in the regulation. We anticipate that over time we may expand our business operations to include operations in the EU, including potentially conducting preclinical and clinical trials. With such expansion, we would be subject to increased governmental regulation in the EU countries in which we might operate, including the GDPR.

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 (possibly significantly) 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.

Whether or not we, or our collaborators, obtain FDA approval for a product, we must obtain the requisite approvals from regulatory authorities in foreign countries prior to the commencement of clinical trials or marketing of the product in those countries. The requirements and process governing the conduct of clinical trials, product licensing, pricing and reimbursement vary from country to country.

If we, or our collaborators, 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.

Pharmaceutical Coverage, Pricing and Reimbursement

Significant uncertainty exists as to the coverage and reimbursement status of any product candidate for which we obtain regulatory approval. In the United States and markets in other countries, sales of any products for which we receive regulatory approval for commercial sale will depend in part on the availability of coverage and adequate reimbursement from third-party payors including government health administrative authorities, managed care providers, private health insurers and other organizations. 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.

Patients who are prescribed medicine for the treatment of their conditions generally rely on third-party payors to reimburse all or part of the associated costs. Patients are unlikely to use our products unless coverage is provided and reimbursement is adequate to cover a significant portion of the cost of our products. Therefore, successful commercialization of our product will depend in part on the availability of third-party payor coverage and adequate reimbursement for the cost of our products and/or payment to the physician for administering our product.

Employees

As of December 31, 2018, we had six full-time employees, two of whom have Ph.D. degrees. In addition, we had engaged nine part-time individual consultants to assist us with managing manufacturing vendors and contract research organizations, project management, legal and regulatory compliance. None of our employees are covered by collective bargaining agreements and we consider relations with our employees to be good.

Research and Development Expenses

Research and development expenses consist primarily of costs associated with the clinical development of topsalysin. Research and development expenses are the primary source of our expenses and totaled $10.7 million, $6.2 million and $3.5 million for the years ended December 31, 2018, 2017 and 2016, respectively.

Corporate Information

We file annual, quarterly, current reports, proxy statements and other information with the Securities and Exchange Commission, or the SEC. Our primary website can be found at http://www.sophirisbio.com. We make available free of charge at this website (under the "Investors — Financial Information" caption) all of our reports filed or furnished pursuant to Section 13(a) or 15(d) of the Securities Exchange Act of 1934, including our Annual Report on Form 10-K, our Quarterly Reports on Form 10-Q and our Current Reports on Form 8-K and amendments to those reports. These reports are made available on the website as soon as reasonably practicable after their filing with, or furnishing to, the SEC. The SEC maintains an internet site that contains our public filings with the SEC and other information regarding the Company, at www.sec.gov. These reports and other information concerning the Company may also be accessed at the SEC's Public Reference Room at 100 F Street, NE, Washington DC 20549. The public may obtain information on the operation of the Public Reference Room by calling the SEC at 1-800-SEC-0330. Furthermore, we also make available on our website free of charge, and in print to any shareholder who requests it, the Committee Charters for our Audit, Compensation, and Governance and Nominating Committees, as well as the Code of Business Conduct and Ethics that applies to all directors, officers and employees of the Company. Amendments to these documents or waivers related to the Code of Business Conduct and Ethics will be made available on our website as soon as reasonably practicable after their execution. The contents of the websites referred to in this paragraph are not incorporated into this Annual Report. Further, our references to the URLs for these websites are intended to be inactive textual reference only.

Our predecessor, Protox Pharmaceuticals Inc., was incorporated in January 2002. We were formed in May 2003 under the predecessor to the British Columbia Business Corporations Act, or the BCBCA, by the amalgamation of Stratos Biotechnologies Inc., Nucleus BioScience Inc. and Brightwave Ventures Inc. under the name SNB Capital Corp. In July 2004, we acquired all the shares of Protox Pharmaceuticals Inc. in a plan of arrangement under the BCBCA and changed its name to Protox Therapeutics Inc. In 2012, we changed our name to Sophiris Bio Inc. We are governed by the Business Corporations Act of British Columbia. Our operations were initially located in Vancouver, British Columbia. In April 2011, we relocated our core activities and headquarters from Vancouver, British Columbia to San Diego, California.

Item 1A. Risk Factors

Risks Related to Our Business and Industry

We will require significant funding to fund our operations, and there is substantial doubt about our ability to continue as a going concern.

This Annual Report on Form 10-K for the year ended December 31, 2018 includes disclosures regarding management's assessment of our ability to continue as a going concern and a report from our independent registered public accounting firm that includes an explanatory paragraph regarding going concern, as our current liquidity position and recurring losses from operations since inception and negative cash flows from operating activities raise substantial doubt about our ability to continue as a going concern.

Our operations have consumed substantial amounts of cash since inception. Since inception, we have raised approximately $146 million from the sale of equity securities in private placements and public offerings, $28 million from the issuance of debt securities and $11 million from the exercise of common share purchase warrants. We will need to continue to spend substantial amounts to continue clinical development of topsalysin. At this point in time we are planning for a Phase 3 clinical trial of topsalysin for the treatment of patients with clinically significant localized prostate cancer subject to regulatory feedback from the U.S. Food and Drug Administration, or FDA, and other foreign regulatory authorities and obtaining additional financing or securing a development partner. We believe the safety and biopsy data from the first administration of topsalysin in our completed Phase 2b clinical trial support moving into a potential Phase 3 clinical trial. We will continue to evaluate whether future clinical development will include an option to administer a second dose of topsalysin as we evaluate the data from the 10 patients who received a second dose in our Phase 2b clinical trial. We are not planning on pursuing other clinical trials, including a second Phase 3 trial for the treatment of patients with benign prostatic hyperplasia, or BPH, unless we secure a development partner to fund such new clinical trials or obtain financing in excess of the financing required for our prostate cancer development program, which is our development priority. There can be no assurance that such funding or a development partner will be available on acceptable terms or at all.

We expect that our existing cash, cash equivalents and securities available-for-sale, together with interest thereon, will be sufficient to fund our operations through September 2019, assuming we do not conduct any new clinical trials. However, changing circumstances may cause us to consume capital significantly faster than we currently anticipate, and we may need to spend more money than currently expected because of circumstances beyond our control. Any new clinical development efforts and our ongoing operations will require significant funding.

We expect to finance future cash needs through public or private equity offerings, debt financings or strategic partnerships and alliances or licensing arrangements. We cannot be certain that additional funding will be available on acceptable terms, or at all. Furthermore, if there remains substantial doubt about our ability to continue as a going concern, investors or other financing sources may be unwilling to provide additional funding on commercially reasonable terms or at all. Subject to limited exceptions, our Loan and Security Agreement with Silicon Valley Bank, or SVB, prohibits us from incurring indebtedness without the prior written consent of SVB. If we are unable to raise additional capital in sufficient amounts or on terms acceptable to us we will need to significantly delay, scale back or discontinue the development or commercialization of topsalysin. We could also be required to seek collaborators for our product candidate on terms that are less favorable than might otherwise be available, relinquish or license on unfavorable terms our rights to our technology or product candidate that we otherwise would seek to develop or commercialize ourselves, significantly reduce expenses, sell assets (potentially at a loss), cease operations altogether, pursue an acquisition of our company at a price that may result in up to a total loss on investment for our shareholders, file for bankruptcy or seek other protection from creditors, or liquidate all of our assets. In addition, if we default under the Loan and Security Agreement with SVB, SVB could foreclose on substantially all of our assets.

Any of the above events could significantly harm our business, prospects, financial condition and results of operations and cause the price of our common shares to decline.

We are a development stage company with no approved products and no revenue from commercialization of any products.

We have not completed the development of any product candidates and, accordingly, have not begun to commercialize, or generate any product revenues from any product candidate. Topsalysin requires significant additional clinical testing and investment prior to seeking marketing approval for either the treatment of localized prostate cancer or the treatment of the symptoms of BPH. On November 10, 2015, we announced final results from our Phase 3 "PLUS-1" study of topsalysin as a treatment for lower urinary tract symptoms of BPH. However, in order to seek regulatory approval for the treatment of the symptoms of BPH, we would be required to conduct a second Phase 3 clinical trial in this indication. At this point in time we have no immediate plans to conduct a second Phase 3 trial in BPH unless we secure a development partner to fund such new clinical trials or obtain financing in excess of the financing required for our prostate cancer development program, which is our development priority.

We are planning a Phase 3 clinical trial of topsalysin for the treatment of patients with clinically significant localized prostate cancer. We will continue to evaluate whether future clinical development will include an option to administer a second dose as we evaluate the safety and biopsy data from the patients who elected to receive a second dose. There have been limited development efforts for a targeted focal therapeutic for patients with clinically significant localized prostate cancer and, therefore, there is significant uncertainty regarding the Phase 3 clinical trial design, including primary endpoint(s), that will be required by the FD, or any foreign regulatory authority. We have had and will continue to have informal discussions with foreign regulatory authorities in Europe where there is more regulatory experience with targeted focal therapy for patients with localized prostate cancer, in order to help inform future clinical trial design. While we believe that we may be able to seek regulatory approval for topsalysin for the treatment of clinically significant localized prostate cancer with one successful Phase 3 clinical trial, we have not discussed late-stage clinical development in this indication with the FDA. The regulatory authorities may ultimately disagree with our assessment of the design, scope and number of clinical trials or other studies before we can submit for regulatory approval. To mitigate these uncertainties, we plan to conduct formal discussions with the FDA and the European Medicines Agency, or EMA. The outcome of these discussions may change our assessment of required clinical trials and our development plans. Any delay in the finalization of the design of a Phase 3 clinical study would delay our development of topsalysin for the treatment of localized prostate cancer.

A commitment of substantial resources by us and potential partners will be required to conduct additional clinical trials for topsalysin to meet applicable regulatory standards, obtain required regulatory approvals, and to successfully commercialize this product candidate for the treatment in either indication. Topsalysin is not expected to be commercially available for either indication for several years, if at all, and any projected timelines for commercialization are subject to a number of factors that are outside our control. There is no assurance that we will be able to commercialize topsalysin within the time periods we expect or that our clinical trials will support the regulatory approvals needed to commercialize topsalysin at all.

We are highly dependent on the success of our sole product candidate, topsalysin, and we may not be able to successfully obtain regulatory or marketing approval for, or successfully commercialize, this product candidate.

To date, we have expended significant time, resources and effort on the development of topsalysin for the treatment of clinically significant localized prostate cancer and for the treatment of lower urinary tract symptoms of BPH, including conducting preclinical and clinical trials. We have no product candidates in our clinical development pipeline other than topsalysin, which we are developing for those two potential indications. Our ability to generate product revenues and to achieve commercial success in the near term will initially depend almost entirely on our ability to successfully raise capital to fund our topsalysin program and to develop, obtain regulatory approval for and then successfully commercialize topsalysin for either of these indications in the United States and the European Economic Area, or EEA. Before we can market and sell topsalysin in the United States or foreign jurisdictions for any indication, we will need to commence and complete additional clinical trials, manage clinical, preclinical, and manufacturing activities, obtain necessary regulatory approvals from the FDA in the United States and from similar foreign regulatory agencies in other jurisdictions, obtain manufacturing supply, build a commercial organization or enter into a marketing collaboration with a third party, and in some jurisdictions, obtain reimbursement authorization, among other things. We cannot assure you that we will be able to successfully complete the necessary clinical trials and/or obtain regulatory approvals and sufficient commercial manufacturing supply for topsalysin in either indication. If we do not receive regulatory approvals, our business, prospects, financial condition and results of operations will be adversely affected. Even if we obtain the regulatory approvals to market and sell topsalysin, we may never generate significant revenues from any commercial sales of topsalysin for several reasons, including because the market for topsalysin may be smaller than we anticipate, topsalysin may not be adopted by physicians and payors or because topsalysin may not be as efficacious or safe as other treatment options. If we fail to successfully commercialize topsalysin, we may be unable to generate sufficient revenues to sustain and grow our business and our business, prospects, financial condition and results of operations will be adversely affected.

Topsalysin may cause undesirable side effects or have other properties that may delay or prevent its regulatory approval or commercialization or limit its commercial potential.

Undesirable side effects caused by topsalysin could cause us or regulatory authorities to interrupt, delay, suspend or terminate clinical trials and could result in a more restrictive label or the delay or denial of marketing approval by the FDA or other regulatory authorities. This, in turn, could limit or prevent us from commercializing topsalysin and generating revenues from its sale. The most common adverse events observed in patients who received topsalysin in our initial Phase 3 clinical trial for the treatment of lower urinary tract symptoms of BPH that were potentially attributable to topsalysin included painful urination, the presence of red blood cells in urine, frequent urination and urinary urgency, fever, and perineal pain. Each of the foregoing adverse events occurred in greater than 5% of the topsalysin population. Further, the incidence of serious AEs, or SAEs, was similar in patients treated with topsalysin and vehicle. There were two SAEs assessed by the investigator as at least possibly related to treatment for topsalysin and one such SAE for vehicle. The topsalysin-related SAEs were moderate events of "acute non-infectious prostatitis" and "fever following prostate procedure" not unexpected manifestations of the intraprostatic cellular destruction and resultant inflammation integral to the topsalysin mechanism of action. The vehicle-related SAE was a mild event of "urinary tract infection." Although the SAEs were moderate and not unexpected, they may not be fully indicative of the adverse events that would be encountered in commercial use or in larger trials. In our completed Phase 2b localized prostate cancer trial a single administration of topsalysin continues to appear safe and well tolerated by patients. No hypersensitivity reactions or other serious systemic reactions to topsalysin were observed after a single administration. Adverse events considered related to topsalysin and occurring in more than one patient were: dysuria (3 patients), urinary retention (3 patients), proctalgia (2 patients), perineal pain (2 patients), nocturia (2 patients), micturition urgency (2 patients) and strangury (2 patients). All adverse events were considered mild and typically resolved within the same day. One event of micturition urgency was considered severe and resolved the same day, two events were considered moderate in severity, one event of perineal pain which resolved within a day and one event of urinary retention was considered moderate and the event was considered resolved after the patient underwent a transurethral resection of the prostate. One of the topsalysin related mild events of stranguary was reported as a serious adverse event (SAE) because the patient was hospitalized overnight for monitoring as was the practice at the site in the UK where the patient had been treated. The event of stranguary resolved the next day and the patient was released from the hospital.

In August 2018, we announced that we had completed an investigation into the death of a patient in the Phase 2b trial for the treatment of localized prostate cancer. It was concluded that the patient death was unlikely to be related to either topsalysin or the injection procedure. On December 17, 2018, we announced the interim safety and tolerability results from the 10 patients who received a second administration of topsalysin from our completed Phase 2b localized prostate cancer trial. A second administration of topsalysin appears to be both safe and well-tolerated by patients. There were no adverse events considered related to topsalysin that were experienced by more than one patient following the second administration. The adverse events that were considered related to topsalysin were typically mild and resolved within two days. Importantly, no hypersensitivity reaction or other serious systemic reactions to topsalysin were observed. Urine function was preserved and there were no reports of sexual dysfunction related to topsalysin.

Results from our future clinical trials could reveal a high and unacceptable severity and prevalence of these or other side effects. In such an event, our trials could be suspended or terminated and the FDA or comparable foreign regulatory authorities could order us to cease further development of or deny approval of topsalysin for its targeted indication. Further, such side effects could affect patient recruitment or the ability of enrolled patients to complete a trial or result in potential product liability claims. Any of these occurrences may have a material and adverse impact on our business, prospects, financial condition and results of operations.

In addition, if topsalysin receives marketing approval for the treatment of the symptoms of BPH or localized prostate cancer, or both, and we or others later identify undesirable side effects caused by topsalysin, a number of significant negative consequences could result, including:

- regulatory authorities may withdraw their approval of topsalysin;
- regulatory authorities may require that we demonstrate a larger clinical benefit by conducting additional clinical trials for approval to offset the risk;
- regulatory authorities may require the addition of labeling statements or warnings that could diminish the usage of the product or otherwise limit the commercial success of topsalysin;
- we may be required to change the way topsalysin is administered;
- we may choose to recall, withdraw or discontinue sale of topsalysin;
- we could be sued and held liable for harm caused to patients;
- we may not be able to enter into collaboration agreements on acceptable terms and execute on our business model; and
- our reputation may suffer.

Any one or a combination of these events could prevent us from achieving or maintaining market acceptance of the affected product or could substantially increase the costs and expenses of commercializing topsalysin, which in turn could delay or prevent us from generating any revenues from the sale of the product, which could significantly harm our business, prospects, financial condition and results of operations.

The clinical trial protocol and design for our completed and any additional future Phase 3 clinical trials of topsalysin may not be sufficient to allow us to submit a BLA to the FDA in the indication of lower urinary tract symptoms of BPH or demonstrate safety or efficacy at the level required by the FDA for product approval.

Our initial Phase 3 clinical trial for the treatment of lower urinary tract symptoms of BPH and any additional Phase 3 clinical trial of topsalysin in this indication use the International Prostate Symptom Score, or IPSS, outcome measure evaluated at total change from baseline over 52 weeks as the primary endpoint. Secondary endpoints include Qmax (maximum urine flow) change from baseline (maximum urine flow) over 52 weeks. The IPSS outcome measure, which is a validated primary efficacy endpoint used to assess the treatment benefit in BPH clinical trials, is a patient recorded, composite assessment that takes into account factors such as ability to empty the bladder, frequency of urination, intermittency of urination and the urgency of urination. The IPSS outcome measure is subjective in nature and requires patients in the trial to accurately and retroactively assess numerous symptoms. The subjective nature of the IPSS outcome measure may make efficacy more difficult to demonstrate than for clinical trials for therapies that can show objective measures of efficacy.

We have not requested a special protocol assessment, or SPA, which drug development companies sometimes use to obtain an agreement with the FDA concerning the design and size of a clinical trial intended to form the primary basis of an effectiveness claim. Without the concurrence of the FDA on an SPA or otherwise, we cannot be certain that the design, conduct and data analysis approach for our initial Phase 3 clinical trial and any future Phase 3 clinical trials has or will generate data sufficient to establish the effectiveness of topsalysin for treatment of BPH symptoms to the FDA's satisfaction, and therefore allow us to submit or receive approval of a Biologics License Application, or BLA for topsalysin in this indication. Specifically, the FDA has not agreed upon the amount of IPSS treatment effect that must be demonstrated in our Phase 3 clinical trials of topsalysin in order for it to grant marketing approval in this indication. Historically, oral medications for the treatment of BPH have shown approximately a 2 point improvement in IPSS between active and control, which was not seen in our PLUS-1 clinical trial. If the FDA requires us, or we otherwise determine, to amend our protocols, change our clinical trial designs, increase enrollment targets or conduct additional clinical trials, our ability to obtain regulatory approval in this indication could be delayed and we could be required to make significant additional expenditures related to clinical development. Further, even if we achieve positive results on the endpoints for a clinical trial, the FDA may disagree with our interpretation of the data and deem the results insufficient to demonstrate efficacy at the level required by the FDA for product approval. It is possible that we may make modifications to the clinical trial protocols or designs of our future clinical trials that delay enrollment or completion of such clinical trials and could delay regulatory approval of topsalysin for the treatment of symptoms of BPH.

Our clinical trials may fail to adequately demonstrate safety and efficacy of topsalysin for either indication being pursued which would prevent or delay regulatory approval and commercialization.

Clinical development is expensive, takes many years to complete and its outcome is inherently uncertain. Failure can occur at any time during the clinical trial process and topsalysin is subject to the risks of failure inherent in drug development. Success in early clinical trials does not mean that later clinical trials will be successful because product candidates in later-stage clinical trials may fail to demonstrate sufficient safety or efficacy despite having progressed through initial clinical testing, even at statistically significant levels. We will be required to demonstrate through well-controlled clinical trials of topsalysin that our product candidate is safe and effective for use in its target indication before we can obtain regulatory approvals for its commercial sale. Companies frequently suffer significant setbacks in late-stage clinical trials, even after earlier clinical trials have shown promising results. Any future clinical trials of topsalysin may not be successful for a variety of reasons, including faults in the clinical trial designs, the failure to enroll a sufficient number of patients, undesirable side effects and other safety concerns and the inability to demonstrate sufficient efficacy. If topsalysin fails to demonstrate sufficient safety or efficacy, we would experience potentially significant delays in, or be required to abandon our development of, topsalysin, which would have a material and adverse impact on our business, prospects, financial condition and results of operations.

We rely on third parties to manufacture topsalysin and we intend to rely on third parties to manufacture commercial supplies of topsalysin, if and when it is approved. The development and commercialization of topsalysin could be stopped or delayed if any such third party fails to provide us with sufficient quantities of topsalysin or the diluent or fails to do so at acceptable quality levels or prices or fails to maintain or achieve satisfactory regulatory compliance.

We do not currently have, nor do we plan to acquire the infrastructure or capability internally to manufacture our clinical drug supplies for use in the conduct of our clinical trials, and we lack the resources and the capability to manufacture topsalysin on a commercial scale. Instead, we rely on our third-party manufacturing partners. Although we have entered into agreements for the manufacture of clinical supplies of topsalysin, our third party manufacturing partners may not perform as agreed, may be unable to comply with cGMP requirements and with FDA, state and foreign regulatory requirements or may terminate their agreements with us. We do not control the manufacturing processes of our third party manufacturers and we are completely dependent on our third party manufacturers for the production of topsalysin in accordance with cGMPs, which include, among other things, quality control, quality assurance and the maintenance of records and documentation.

We have entered into an agreement with Boehringer Ingelheim RCV GmbH & Co KG, or BI, to manufacture topsalysin drug substance. We have completed scale-up up to the commercial batch size for topsalysin drug substance, but the finalization of the commercial fill finish process for the production of drug product is still underway. In addition, we recently completed a project to optimize the formulation of topsalysin drug product. We have incurred and will continue to incur significant costs to ensure that the new drug product formulation is comparable with our previous drug product formulation. There is no guarantee that the new drug product formulation will obtain the same clinical results as our old drug formulation.

We have selected Vetter Pharma International GmbH to work on the completion of the specifications for the fill finish process for the production of reformulated topsalysin drug product and to supply clinical trial drug product material. We are currently in the process of negotiating a long-term contract with Vetter. We have, and we will continue to incur significant costs in connection with the technology transfer and manufacturer of clinical drug supplies. Our purchase orders under our manufacturing contracts either cannot be cancelled or can only be cancelled with the payment of financial penalties. Any delay in the technology transfer to Vetter or completion of fill finish for our future clinical trial supply would result in future delays in our ability to commence additional clinical trials.

BI historically procured an ingredient used in our former diluent formulation for use with topsalysin drug product from a multinational industrial biotech company which is a single source supplier, on a purchase order basis. Our new drug product formulation does not use this single source provider ingredient in the diluent formulation. If we are required to revert back to our old drug product formulation and if our single source provider is unable to or decides to no longer supply BI or us with an ingredient for the diluent, we could experience delays in obtaining product for clinical trials until we procured another source or until we reformulate the product and we may be required to contract with another source in order to assure adequate commercial supply.

If our third-party manufacturers cannot successfully manufacture material that conforms to our specifications and the applicable regulatory authorities' strict regulatory requirements, or pass regulatory inspection, they will not be able to secure or maintain regulatory approval for the manufacturing facilities. In addition, we have no control over the ability of any third-party manufacturers to maintain adequate quality control, quality assurance and qualified personnel. If the FDA or any other applicable regulatory authorities do not approve these facilities for the manufacture of our products or if they withdraw any such approval in the future, or if our suppliers or third-party manufacturers decide they no longer want to supply our biologic or manufacture our products, we may need to find alternative manufacturing facilities, which would significantly impact our ability to develop, obtain regulatory approval for or market our products.

The facilities used by our third-party manufacturers to manufacture topsalysin and any other potential product candidates that we may develop in the future must be approved by the applicable regulatory authorities, including the FDA, pursuant to inspections that will be conducted after we submit our BLA to the FDA. Further, manufacturers are subject to ongoing periodic unannounced inspection by the FDA and other governmental authorities to ensure strict compliance with government regulations. Currently, our contract manufacturers are located outside the United States and the FDA has recently increased the number of foreign drug manufacturers which it inspects. As a result, these third-party manufacturers may be subject to increased scrutiny.

Topsalysin is manufactured by starting with cells which are stored in a cell bank. We have one master cell bank and multiple working cell banks and believe we would have adequate backup should any cell bank be lost in a catastrophic event. However, it is possible that we could lose multiple cell banks and have our manufacturing severely impacted by the need to replace the cell banks. Also, if we were to experience an unexpected loss of topsalysin supply, we could experience delays in our future clinical trials as our third party manufacturers would need to manufacture additional topsalysin and would need sufficient lead time to schedule a manufacturing slot. This is due to the fact that, given its nature, topsalysin cannot be manufactured in a facility at the same time as other biologics.

The manufacture of biopharmaceutical products is complex and requires significant expertise and capital investment, including the development of advanced manufacturing techniques and process controls. We and our contract manufacturers must comply with cGMP regulations and guidelines. Manufacturers of biopharmaceutical products often encounter difficulties in production, particularly in scaling up and validating initial production and contamination. These problems include difficulties with production costs and yields, quality control, including stability of the product, quality assurance testing, operator error, shortages of qualified personnel, as well as compliance with strictly enforced federal, state and foreign regulations. Furthermore, if microbial, viral or other contaminations are discovered in our products or in the manufacturing facilities in which our products are made, such manufacturing facilities may need to be closed for an extended period of time to investigate and remedy the contamination. We cannot assure you that any stability or other issues relating to the manufacture of any of our products will not occur in the future. Additionally, our manufacturer may experience manufacturing difficulties due to resource constraints or as a result of labor disputes or unstable political environments. If our manufacturer were to encounter any of these difficulties, or otherwise fail to comply with their contractual obligations, our ability to provide any product candidates to patients in clinical trials would be jeopardized. Any delay or interruption in the supply of clinical trial supplies could delay the completion of clinical trials, increase the costs associated with maintaining clinical trial programs and, depending upon the period of delay, require us to commence new clinical trials at additional expense or terminate clinical trials completely.

Any adverse developments affecting clinical or commercial manufacturing of our products may result in shipment delays, inventory shortages, lot failures, product withdrawals or recalls, the need to reformulate our product or other interruptions in the supply of our products. We may also have to take inventory write-offs and incur other charges and expenses for products that fail to meet specifications, undertake costly remediation efforts or seek more costly manufacturing alternatives. Accordingly, failures or difficulties faced at any level of our supply chain could materially adversely affect our business and delay or impede the development and commercialization of any of our products or product candidates and could have a material adverse effect on our business, prospects, financial condition and results of operations.

We may seek a partner for the continued development and commercialization of topsalysin. If we seek a partner and are unable to find a partner or such partnership is unsuccessful, we may be unable to commercialize topsalysin.

We may seek a third-party partner for financial and scientific resources for the further clinical development and commercialization of topsalysin. There is no assurance that we will be able to find such a partner and, if we do, we may have to relinquish a significant portion of the future economic value of topsalysin to such partner. Also, a partner will likely significantly limit our control over the course of clinical development and/or commercialization of topsalysin. Our ability to recognize revenue from a successful partnering arrangement of the sort we are contemplating may be impaired by several factors, including:

- a partner may shift its priorities and resources away from topsalysin due to many reasons, including a change in business strategy, a merger, acquisition, sale or downsizing of its company or business unit;
- successfully identifying a new partner and negotiating an agreement could be more difficult or the terms less advantageous because we have already established a partnership for Japan;
- a partner may have the ability to unilaterally cease development of topsalysin;
- a partner may change the success criteria for topsalysin as a treatment for the symptoms of BPH or as a treatment for clinically significant localized prostate cancer thereby delaying or ceasing clinical development of topsalysin;
- a partner could develop a product that competes, either directly or indirectly, with topsalysin;
- a partner with commercialization obligations may not commit sufficient financial or human resources to the marketing, distribution or sale of topsalysin;
- a dispute could arise between us and a partner concerning the research, development or commercialization of topsalysin which could delay or terminate development and, possibly, result in costly litigation or arbitration which may divert management attention and resources; and
- a partner may use our proprietary information or intellectual property in such a way as to invite litigation from a third party or fail to maintain or prosecute intellectual property rights such that our rights are jeopardized.

In addition, any adverse developments that occur during any clinical trials conducted by or under the supervision of a partner may affect our ability to obtain regulatory approval or commercialize topsalysin.

Further, if a partnership terminates an agreement with us or is otherwise unsuccessful, we may need to seek out and establish an alternative partnership. This may not be possible, or we may not be able to do so on terms which are acceptable to us, in which case, it may be necessary for us to cease the development of topsalysin or conduct the remaining clinical development on our own and with our own funds.

Any of these events would have a material adverse effect on our results of operations and financial condition.

Topsalysin is subject to extensive regulation, and we may not obtain regulatory approvals for topsalysin.

The clinical development, manufacturing, labeling, packaging, storage, tracking, recordkeeping, advertising, promotion, export, import, marketing and distribution and other possible activities relating to our product candidate are, and for any other biologic or drug candidate that we may develop will be, subject to extensive regulation by the FDA in the United States and other regulatory agencies in foreign jurisdictions. Topsalysin is subject to regulation in the United States as a biologic. Biologics require the submission of a BLA, and we are not permitted to market topsalysin in the United States until we obtain approval from the FDA of a BLA. To market topsalysin in the EEA, which includes the 28 member states of the European Union plus Norway, Liechtenstein and Iceland, we must submit a Marketing Authorization Application, or MAA, to the EMA, for approval under the EMA's centralized procedure, which if the marketing authorization is granted, will enable us to market the product throughout the entire territory of the EEA. A BLA or MAA must be supported by extensive clinical and preclinical data, as well as extensive information regarding chemistry, manufacturing and controls, or CMC, sufficient to demonstrate the safety and effectiveness of the applicable product candidate to the satisfaction of FDA and EMA, respectively.

Regulatory approval of a BLA or an MAA is not guaranteed, and the approval process is expensive and will take several years. The FDA and foreign regulatory entities also have substantial discretion in the approval process. The number and types of preclinical studies and clinical trials that will be required for BLA or MAA approval varies depending on the product candidate, the disease or the condition that the product candidate is designed to target and the regulations applicable to any particular product candidate. Despite the time and expense associated with preclinical studies and clinical trials, failure can occur at any stage, and we could encounter problems that cause us to repeat or perform additional preclinical studies or clinical trials or generate additional CMC data. The FDA, EMA and similar foreign authorities could delay, limit or deny approval of a product candidate for many reasons, including because they:

- may not deem our product candidate to be adequately safe and effective;
- may not find the data from our preclinical studies and clinical trials or CMC data to be sufficient to support a claim of safety and efficacy;
- may not approve the manufacturing processes or facilities associated with our product candidate;
- may conclude that we have not sufficiently demonstrated long-term stability of the formulation of the drug product for which we are seeking marketing approval;
- may change approval policies (including with respect to our product candidate's class of biologics) or adopt new regulations; or
- may not accept a submission due to, among other reasons, the content or formatting of the submission.

Obtaining approval of a BLA is a lengthy, expensive and uncertain process. As part of the U.S. Prescription Drug User Fee Act, the FDA has a goal to review and act on a percentage of all submissions in a given time frame. The general review goal for a BLA is 12 months from the submission date for a standard application and eight months from the submission date for a priority review application. The FDA's review goals are subject to change, and it is unknown whether the review of a BLA for topsalysin will be completed within the FDA's target timelines or will be delayed. Moreover, the duration of the FDA's review may depend on the number and types of other BLAs that are submitted to the FDA around the same time period or are pending. Generally, public concern regarding the safety of drug products could delay or limit our ability to obtain regulatory approval, result in the inclusion of unfavorable information in our labeling, or require us to undertake other activities that may entail additional costs.

We have not submitted an application for approval or obtained FDA approval for any product. This lack of experience may impede our ability to obtain FDA approval in a timely manner, if at all, for topsalysin. In addition, failure to comply with FDA and other applicable U.S. and foreign regulatory requirements, either before or after product approval, may subject us to administrative or judicially imposed sanctions, including warning letters, civil and criminal penalties, injunctions, withdrawal of approved products, product seizure or detention, product recalls, total or partial suspension of production, and refusal to approve pending BLAs or supplements to approved BLAs.

Even if we believe that data collected from our preclinical studies and clinical trials of our product candidate are promising, our data may not be sufficient to support marketing approval by the FDA or any foreign regulatory authority, or regulatory interpretation of these data and procedures may be unfavorable. In addition, the FDA's regulatory review of BLAs for product candidates intended for widespread use by a large proportion of the general population is becoming increasingly focused on safety, which may lead to increased scrutiny of the safety data we submit in any BLA for topsalysin. Even if approved, a product candidate may not be approved for all indications requested and such approval may be subject to limitations on the indicated uses for which the biologic may be marketed, restricted distribution methods or other limitations. Our business and reputation may be harmed by any failure or significant delay in obtaining regulatory approval for the sale of our product candidate. We cannot predict when or whether regulatory approval will be obtained for any product candidate we develop.

To market any biologics outside of the United States, we and current or future collaborators must comply with numerous and varying regulatory and compliance related requirements of other countries. Approval procedures vary among countries and can involve additional product testing and additional administrative review periods, including obtaining reimbursement and pricing approval in select markets. The time required to obtain approval in other countries might differ from that required to obtain FDA approval. The regulatory approval process in other countries may include all of the risks associated with FDA approval as well as additional, presently unanticipated, risks. Regulatory approval in one country does not ensure regulatory approval in another, but a failure or delay in obtaining regulatory approval in one country may negatively impact the regulatory process in others, including the risk that our product candidates may not be approved for all indications requested and that such approval may be subject to limitations on the indicated uses for which the drug may be marketed.

Delays in the commencement or completion of clinical testing could significantly impact our product development costs and will delay our ability to pursue regulatory approval and, in turn, our ability to generate any product revenues.

Although we have completed the first of two required Phase 3 clinical trials of topsalysin for the treatment for the lower urinary tract symptoms of BPH and completed a Phase 2b open-label clinical trial for the treatment of localized low to intermediate risk prostate cancer, we do not know whether or when we will be able to fund any additional clinical trials for either the treatment of clinically significant localized prostate cancer or the treatment of the symptoms of BPH, or if any future trials will be completed on time, or at all.

Further, the commencement or completion of clinical trials can be delayed for a variety of reasons, including delays in or related to:

- raising sufficient capital or securing a development partner to fund future clinical trials, including a Phase 3 clinical trial of topsalysin for the treatment of clinically significant localized prostate cancer and a second Phase 3 clinical trial for the treatment of the symptoms of BPH;
- obtaining regulatory approval, or feedback on trial design necessary, to commence a clinical trial;
- identifying, recruiting and training suitable clinical investigators;
- identifying, recruiting and enrolling suitable patients to participate in a clinical trial;
- catastrophic loss of drug product due to shipping delays or delays in customs in connection with delivery of drug product to foreign countries for use in clinical trials;
- reaching agreement on acceptable terms with prospective contract research organizations, or CROs, and clinical trial sites, the terms of which can be subject to extensive negotiation and may vary significantly among different CROs and clinical trial sites;
- completing the reformulation of topsalysin drug substance and drug product;
- achieving commercial-scale manufacturing of topsalysin;
- validating a commercial fill finish process for topsalysin drug product and obtaining sufficient quantities of topsalysin for use in any future Phase 3 clinical trials;
- having patients complete a trial or return for post-treatment follow-up;
- adding new clinical trial sites;
- failure to conduct the clinical trial in accordance with regulatory requirements or our clinical protocols;
- failure to demonstrate a benefit from using a drug, changes in governmental regulations or administrative actions;
- unforeseen safety issues or any determination that a clinical trial presents unacceptable health risks;
- obtaining institutional review board, or IRB, approval to conduct a clinical trial at a prospective site; and
- retaining patients who have initiated a clinical trial but may withdraw due to adverse side effects from the therapy, insufficient efficacy, fatigue with the clinical trial process or personal issues.

Any delays in the commencement or completion of our clinical trials will delay our timeline to obtain regulatory approval for our product candidate. In addition, many of the factors that cause, or lead to, a delay in the commencement of clinical trials may also ultimately lead to the denial of regulatory approval for a product candidate. We do not expect to commence enrollment of our second required Phase 3 clinical trial for the treatment of the lower urinary tract symptoms of BPH unless we secure a development partner to fund such clinical trial or we obtain financing in excess of the financing required for our localized prostate cancer development program, which is our development priority.

We may face competition to enroll localized prostate cancer and BPH patients in our future clinical trials from other clinical trials for other sponsors including potential competitors. Patient enrollment, a significant factor in the timing of clinical trials, is affected by many factors including the size and nature of the patient population, the proximity of patients to clinical sites, the eligibility criteria for the trial, the design of the clinical trial, competing clinical trials and clinicians' and patients' perceptions as to the potential advantages of the drug being studied in relation to other available therapies, including any new drugs that may be approved for the indications we are investigating. Delays in enrollment in any future clinical trials of topsalysin would result in delays in our ability to pursue regulatory approval of topsalysin.

Changes in regulatory requirements and guidance also may occur and we may need to amend clinical trial protocols to reflect these changes. Amendments may require us to resubmit our clinical trial protocols to IRBs for re-examination, which may impact the costs, timing and successful completion of a clinical trial. If we experience delays in the completion of, or if we must terminate, any clinical trial of topsalysin, our ability to obtain regulatory approval for that product candidate will be delayed and the commercial prospects, if any, for the product candidate may be harmed. If we ultimately commercialize topsalysin, other therapies for the same indications may have been introduced to the market during the period we have been delayed and such therapies may have established a competitive advantage over our product candidates.

We have relied upon and expect to rely upon multiple CROs to conduct and oversee any future clinical trials for topsalysin. If any of our CROs does not meet our deadlines or otherwise conduct the trials as required or if any CRO experiences regulatory compliance issues we may not be able to obtain regulatory approval for or commercialize our product candidate when expected or at all.

We have used multiple CROs for our clinical trials of topsalysin and expect to rely upon CROs for any future clinical trials. We also rely upon medical institutions, clinical investigators and contract laboratories to conduct our trials in accordance with our clinical protocols and in accordance with applicable legal and regulatory requirements. These third parties play a significant role in the conduct of these trials and the subsequent collection and analysis of data from the clinical trials. There is no guarantee that any such third party will devote adequate time and resources to our clinical trial. If any of our CROs or any other third parties upon which we rely for administration and conduct of our clinical trials do not successfully carry out their contractual duties or obligations or fail to meet expected deadlines, if they need to be replaced or if the quality or accuracy of the clinical data they obtain is compromised due to the failure to adhere to our clinical protocols or regulatory requirements or if they otherwise perform in a substandard manner, our clinical trials may be extended, delayed, suspended or terminated, and we may not be able to complete development of and ultimately obtain approval for and successfully commercialize topsalysin. We will rely heavily on these third parties for the execution of our future clinical trials and will control only certain aspects of their 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 CROs does not relieve us of our regulatory responsibilities.

We and our CROs are required to comply with current Good Clinical Practice, or GCP, which are regulations and guidelines enforced by the FDA, the competent authorities of the Member States of the EEA and comparable foreign regulatory authorities for products in clinical development. Regulatory authorities enforce these GCP regulations through periodic inspections of clinical trial sponsors, principal investigators and clinical trial sites. If we or any of our CROs fail to comply with applicable GCP regulations, the clinical data generated in our clinical trials may be deemed unreliable and our submission of marketing applications may be delayed or the FDA may require us to perform additional clinical trials before approving our marketing applications. We cannot assure you that, upon inspection, the FDA will determine that any of our clinical trials comply or complied with applicable GCP regulations. In addition, our clinical trials must be conducted with product produced under the current Good Manufacturing Practice, or cGMP, regulations enforced by the FDA, and our clinical trials require a large number of test subjects. Our failure to comply with these regulations may require us to repeat clinical trials, which would delay the regulatory approval process. Moreover, our business may be implicated if any of our CROs violates federal or state fraud and abuse or false claims laws and regulations or healthcare privacy and security laws.

Switching or adding CROs can involve substantial cost and require extensive management time and focus. In addition, there is a natural transition period when a new CRO commences work. As a result, delays may occur, which can materially impact our ability to meet our desired clinical development timelines. Though we carefully manage our relationship with our CROs, there can be no assurance that we will not encounter such challenges or delays in the future or that these delays or challenges will not have a material adverse impact on our business, prospects, financial condition or results of operations.

Any adverse developments that occur during any clinical trials conducted by Kissei may affect our ability to obtain regulatory approval or commercialize topsalysin.

Kissei retains the rights to develop and commercialize topsalysin in Japan for the treatment of the symptoms of BPH, prostate cancer, prostatitis or other diseases of the prostate. If serious adverse events occur during any clinical trials Kissei decides to conduct with respect to topsalysin, the FDA and other regulatory authorities may delay, limit or deny approval of topsalysin 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 topsalysin and a new and serious safety issue is identified in connection with clinical trials conducted by Kissei, 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 topsalysin. Kissei is not currently conducting any clinical trials with topsalysin for the treatment of BPH, prostate cancer, prostatitis or other diseases of the prostate.

We face significant competition from other pharmaceutical and biotechnology companies and from minimally invasive surgical therapies and surgical alternatives, and our operating results will suffer if we fail to compete effectively.

The biotechnology and pharmaceutical industries are intensely competitive. We have competitors both in the United States and international markets, including major multinational pharmaceutical companies, biotechnology companies and universities and other research institutions. Many of our competitors have substantially greater financial, technical and other resources, such as larger research and development staff, experienced marketing and manufacturing organizations and well-established sales forces. Additional mergers and acquisitions in the biotechnology and pharmaceutical industries may result in even more resources being concentrated in our competitors. Competition may increase further as a result of advances in the commercial applicability of technologies and greater availability of capital for investment in these industries. Our competitors may succeed in developing, acquiring or licensing on an exclusive basis, products that are more effective, easier to administer and/or less costly than topsalysin.

We expect that topsalysin will compete with the current treatment options for the treatment of clinically significant localized prostate cancer, which include surgical options such as laparoscopic and radical prostatectomy or radiation. In addition, there are other focal targeted therapies which are gaining traction that are currently in clinical development or have been recently approved which include: brachytherapy, cryotherapy, high focused ultrasound, cyber knife, radio frequency ablation, laser ablation and TOOKAD, a vascular –targeted photodynamic therapy recently approved by the EMA. In addition, in January 2018, Nymox Pharmaceuticals announced top-line five year clinical trial biopsy data from the intraprostatic administration of their investigational therapy NX-1207 (fexapotide triflutate) in patients with low grade localized (T1c) prostate cancer.

We expect that topsalysin will compete with the current treatment options for the symptoms of BPH, which include oral drug therapy and surgery. Oral drug therapies include (a) alpha-blockers, such as tamsulosin (marketed under various trade names by numerous companies, including as Flomax® by Astellas Pharma), alfuzosin (marketed in the United States by Sanofi as Uroxatral®), doxazosin (marketed by Pfizer as Cardura® and Cardura® XL) and silodosin (marketed by Watson Pharmaceuticals as Rapaflo® in the United States), (b) 5-alpha reductase inhibitors, such as dutasteride (marketed by GlaxoSmithKline plc as Avodart®) and finasteride (marketed by Merck & Co., Inc. as Proscar®), (c) combinations of a-blockers and 5-alpha reductase inhibitors such as tamsulosin and dutasteride (marketed by GSK as Jalyn®) and (d) tadalafil (marketed as Cialis® by Eli Lilly), a PDE5 inhibitor. Several minimally invasive surgical therapies, or MIST, are available, including transurethral microwave thermotherapy, or TUMT, transurethral needle ablation, or TUNA, photo-selective vaporization of prostate, holmium laser enucleation of the prostate, transurethral electrovaporization of the prostate, interstitial laser coagulation, and the UroLift® system (marketed by NeoTract, Inc.), which is an implant delivered into the body via a small needle and designed to hold prostate tissue out of the way of the blocked urethra.. Surgery for BPH treatment is usually considered in patients who fail drug therapy as a result of side effects or inadequate relief of symptoms, have refractory urinary retention, or have recurrent urinary tract infections. Alternatively, surgery may be the initial treatment in patients with severe urinary symptoms. Surgical procedures for BPH include transurethral resection of the prostate, as well as other procedures such as transurethral incision of the prostate and transurethral vaporization of the prostate. Nymox Pharmaceuticals announced that it plans to submit a New Drug Application for Fexapotide Triflutate for the treatment of BPH in the United States. In December 2017, Procept BioRobotics received FDA clearance for its AquaBeam System, a waterjet ablation therapy for endoscopic resection of prostate tissue. In addition, there are other treatments that are currently in clinical development for the treatment of the symptoms of BPH. Light Sciences Oncology Inc.'s talaporfin sodium is currently in Phase 2 clinical trials.

The availability and price of our competitors' products and procedures could limit the demand, and the price we are able to charge, for topsalysin. Further, our lack of data on long term disease progression 5 to 10 years following administration of topsalysin in order to demonstrate that our product is comparable to more radical therapies such as prostatectomy and/or radiation could limit demand for topsalysin for focal treatment of localized prostate cancer. We will not successfully execute on our business objectives if the market acceptance of topsalysin is inhibited by price competition, if physicians are reluctant to switch from existing products or procedures to topsalysin or if physicians switch to other new products or surgeries or choose to reserve topsalysin for use in limited patient populations. In addition, established pharmaceutical companies may invest heavily to accelerate discovery and development of novel compounds or to in-license and develop novel compounds that could make topsalysin obsolete.

Any new product that competes with an approved product must demonstrate compelling advantages in efficacy, convenience, tolerability and safety in order to be approved and overcome price competition and to be commercially successful. Accordingly, our competitors may succeed in obtaining patent protection, obtaining FDA approval or discovering, developing and commercializing products before we do, which would have a material adverse impact on our business. The inability to compete with existing products or subsequently introduced products would have a material adverse impact on our business, prospects, financial condition and results of operations.

Even if we obtain and maintain approval for topsalysin from the FDA in either indication, we may never obtain approval for topsalysin outside of the United States, which would limit our market opportunities and adversely affect our business.

Sales of topsalysin outside of the United States will be subject to foreign regulatory requirements governing clinical trials and marketing approval. Even if the FDA grants marketing approval for a product candidate, comparable regulatory authorities of foreign countries must also approve the manufacturing and marketing of the product candidates 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. In many countries outside the United States, a product candidate must be approved for reimbursement before it can be approved for sale in that country. In some cases, the price that we intend to charge for our products is also subject to approval. We may decide to submit an MAA to the EMA for approval in the EEA. As with the FDA, obtaining approval of an MAA from the EMA is a similarly lengthy and expensive process and the EMA has its own procedures for approval of product candidates. Even if a product is approved, the FDA or the EMA, as the case may be, may limit the indications for which the product may be marketed, require extensive warnings on the product labeling or require expensive and time-consuming clinical trials or reporting as conditions of approval. Regulatory authorities in countries outside of the United States and the EEA also have requirements for approval of drug candidates with which we must comply prior to marketing in those countries. 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. Further, clinical trials conducted in one country may not be accepted by regulatory authorities in other countries and regulatory approval in one country does not ensure approval in any other country, while a failure or delay in obtaining regulatory approval in one country may have a negative effect on the regulatory approval process in others. Also, regulatory approval for any of our product candidates may be withdrawn. 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 topsalysin will be harmed and our business will be adversely affected.

We will be, with respect to any product candidate for which we obtain FDA approval, subject to ongoing FDA obligations and continued regulatory review, which may result in significant additional expense.

Any regulatory approvals that we obtain for our product candidate may also be subject to limitations on the approved indicated uses for which the product may be marketed or to the conditions of approval, or contain requirements for potentially costly post-marketing testing, including post-marketing studies and clinical trials and surveillance to monitor the safety and efficacy of the product candidate. These requirements include submissions of safety and other post-marketing information and reports, registration, as well as continued compliance with cGMPs for marketed drugs and drugs used in clinical trials and GCPs for any clinical trials that we conduct post-approval. In addition, if the FDA or a comparable foreign regulatory authority, like the EMA, approves a product candidate, the manufacturing processes, labeling, packaging, distribution, adverse event reporting, storage, advertising, promotion, import, export, tracking and recordkeeping for the product will be subject to extensive and ongoing regulatory requirements. For example, 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 liability. Later discovery of previously unknown problems with a product, 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 the product, 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 our strategic partners, or suspension or revocation of product license approvals;
- product seizure or detention, or refusal to permit the import or export of products; and
- injunctions, the imposition of civil or criminal penalties, or exclusions.

The FDA's policies may change and additional government regulations may be enacted that could prevent, limit or delay regulatory approval of our product candidates. If we are slow or unable to adapt to changes in existing requirements or the adoption of new requirements or policies, or if we are not able to maintain regulatory compliance, we may lose any marketing approval that we may have obtained and we may not achieve or sustain profitability, which would have a material adverse effect on our business, prospects, financial condition and results of operations.

Moreover, the federal Drug Supply Chain Security Act, imposes obligations on manufacturers of pharmaceutical products, among others, related to product tracking and tracing. Among the requirements of this federal legislation, manufacturers are required to provide certain information regarding the drug product to individuals and entities to which product ownership is transferred, label drug product with a product identifier, and keep certain records regarding the drug product. Further, manufacturers have drug product investigation, quarantine, disposition, and notification responsibilities related to counterfeit, diverted, stolen, and intentionally adulterated products, as well as products that are the subject of fraudulent transactions or which are otherwise unfit for distribution such that they would be reasonably likely to result in serious health consequences or death.

If we fail to comply with health care laws, we could face substantial penalties and our business, operations and financial condition could be adversely affected.

Even though we do not and will not control referrals of healthcare services or bill directly to Medicare, Medicaid or other third-party payors, certain federal and state healthcare laws and regulations, including those pertaining to fraud and abuse and patients' rights, are and will be applicable to our business. We could be subject to healthcare regulation by both the federal government and the states in which we conduct our business. The federal and state health care laws and regulations that may affect our ability to operate include, without limitation: anti-kickback statutes, false claims statutes, patient data privacy and security laws, and physician sunshine laws and regulations, many of which may become more applicable if our product candidates are approved and we begin commercialization. If our operations are found to be in violation of any of these laws or regulations, we may be subject to significant penalties, including administrative, civil and criminal penalties, damages, fines, disgorgement, imprisonment, exclusion from participation in federal healthcare programs, and 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, as well as contractual damages, reputational harm, diminished profits and future earnings, and the curtailment or restructuring of our operations. Any such penalties could adversely affect our ability to operate our business and our financial results. Any action against us for violation of these laws and regulations, even if we successfully defend against it, could cause us to incur significant legal expenses and divert our management's attention from the operation of our business. Moreover, achieving and sustaining compliance with these laws and regulations may prove costly.

We will need to increase the size of our organization and the scope of our outside vendor relationships, and we may experience difficulties in managing growth.

As of December 31, 2018, we had six full-time employees. In addition, we had engaged nine part-time individual consultants to assist us with managing manufacturing vendors and CROs, project management, legal and regulatory compliance. We will need to expand our managerial, operational, financial and other resources in order to manage our future operations and clinical trials, continue our research and development activities, and commercialize our product candidate. Our management and scientific personnel, systems and facilities currently in place may not be adequate to support our future growth. Our need to effectively manage our operations, growth and various projects requires that we:

- manage our clinical trials effectively;
- manage our internal development efforts effectively while carrying out our contractual obligations to licensors, contractors and other third parties;
- continue to improve our operational, financial and management controls and reporting systems and procedures;
- attract and retain sufficient numbers of talented employees; and
- manage our regulatory compliance oversight and infrastructure.

To date, we have utilized the services of third-party vendors to perform tasks including clinical trial management, statistics and analysis, regulatory affairs, formulation development and other drug development functions. Our growth strategy may also entail expanding our group of contractors or consultants to implement these tasks going forward. Because we rely on numerous consultants, effectively outsourcing many key functions of our business, we will need to be able to effectively manage these consultants to ensure that they successfully carry out their contractual obligations and meet expected deadlines. However, 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 for our product candidate 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 be unable to successfully implement the tasks necessary to further develop and commercialize our product candidate and, accordingly, may not achieve our research, development and commercialization goals.

Our limited operating history makes evaluating our business and future prospects difficult.

Our predecessor, Protox Pharmaceuticals Inc., was incorporated in January 2002. We were formed in May 2003 under the predecessor to the British Columbia Business Corporations Act, or the BCBCA, by the amalgamation of Stratos Biotechnologies Inc., Nucleus BioScience Inc. and Brightwave Ventures Inc. under the name SNB Capital Corp. In July 2004, we acquired all the shares of Protox Pharmaceuticals Inc. in a plan of arrangement under the BCBCA and changed its name to Protox Therapeutics Inc. In 2011, we formed a wholly-owned U.S. subsidiary incorporated in Delaware, Protox Therapeutics Corp. In 2012, we changed our name to Sophiris Bio Inc. and changed the name of our subsidiary to Sophiris Bio Corp. In 2012, Sophiris Bio Corp. formed a wholly-owned subsidiary incorporated in Delaware, Sophiris Bio Holding Corp. We face considerable risks and difficulties as a company with limited operating history, particularly as a consolidated entity with an operating subsidiary that also has a limited operating history. If we do not successfully address these risks, our business, prospects, operating results and financial condition will be materially and adversely harmed. Our limited operating history makes it particularly difficult for us to predict our future operating results and appropriately budget for our expenses. In the event that actual results differ from our estimates or we adjust our estimates in future periods, our operating results and financial position could be materially affected. We have limited experience as a consolidated operating entity and have not yet demonstrated an ability to successfully overcome many of the risks and uncertainties frequently encountered by companies in new and rapidly evolving fields, particularly in the pharmaceutical or biotechnology areas.

The terms of our Loan and Security Agreement with Silicon Valley Bank require us to meet certain operating covenants and place restrictions on our operating and financial flexibility. If we raise additional capital through debt financing, the terms of any new debt could further restrict our ability to operate our business.

In September 2017, we entered into a Loan and Security Agreement with SVB. This loan is secured by a lien covering all of our assets, excluding intellectual property, and we also pledged as collateral all of our equity interests in Sophiris Bio Corp. and Sophiris Bio Holding Corp.

While any amounts are outstanding under the Loan and Security Agreement, we are subject to a number of affirmative and restrictive covenants, including covenants regarding dispositions of property, business combinations or acquisitions, incurrence of additional indebtedness and transactions with affiliates, among other customary covenants. We are also restricted from paying dividends or making other distributions or payments on our capital stock, subject to limited exceptions. Upon the occurrence of an event of default by us under the Loan and Security Agreement, SVB will have customary acceleration, collection and foreclosure remedies.

Further, if we are liquidated, SVB's right to repayment would be senior to the rights of the holders of our common shares to receive any proceeds from the liquidation. SVB could declare a default under the loan upon the occurrence of any event that SVB interprets 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 SVB of an event of default could significantly harm our business and prospects and could cause the price of our common shares to decline. If we raise any additional debt financing, the terms of such additional debt could further restrict our operating and financial flexibility.

Our ability to generate revenues from topsalysin will be subject to attaining significant market acceptance among physicians, patients and healthcare payors.

Topsalysin, if approved in either indication for which we are currently pursuing development or any other indication, may not attain market acceptance among physicians, patients, healthcare payors or the medical community. We believe that the degree of market acceptance and our ability to generate revenues from topsalysin will depend on a number of factors, including:

- timing of market introduction of our products as well as competitive procedures or drugs;
- efficacy and safety of topsalysin and the availability of data to demonstrate long-term efficacy;
- the clinical indication(s) for which topsalysin is approved;
- continued projected growth of the urological disease markets, including incidence of localized prostate cancer with tumors amenable to focal therapy, and incidence of BPH;
- continued adoption and improvement of imaging and diagnostic tools, including MRI-guided biopsies and molecular tests, to assess and identify candidates for focal treatment of localized prostate cancer;
- acceptance by patients, primary care specialists and key specialists, including urologists and oncologists for localized prostate cancer and urologists for BPH;
- potential or perceived advantages or disadvantages of topsalysin over alternative treatments, for prostate cancer and BPH including cost of treatment and relative convenience and ease of administration, the amount of time for a patient to notice the effects of the treatment and length of sustained benefits from treatment;
- strength of sales, marketing and distribution support;
- the price of topsalysin, both in absolute terms and relative to alternative treatments;
- the effect of current and future healthcare laws;

- availability of coverage and adequate reimbursement and pricing from government and other third-party payors for MRI-guided biopsies and other diagnostic tools and for topsalysin procedures; and

- product labeling or product insert requirements of the FDA or other regulatory authorities.

If topsalysin is approved in either or both indications but fails to attain market acceptance by physicians, patients, health care payors, or the medical community, we may not be able to generate significant revenue to achieve or sustain profitability, which would have a material adverse effect on our business, prospects, financial condition and results of operations.

Coverage and reimbursement may not be available, or may be available at only limited levels, for topsalysin, which could make it difficult for us to sell topsalysin profitably.

Market acceptance and sales of topsalysin will depend in large part on global coverage and reimbursement policies and may be affected by future healthcare reform measures, both in the United States and other key international markets. Patients who are prescribed medicine for the treatment of their conditions generally rely on third-party payors to reimburse all or part of the costs associated with their prescription drugs. Patients are unlikely to use our products unless coverage is provided and reimbursement is adequate to cover a significant portion of the cost of our products. Therefore, successful commercialization of our product will depend in part on the availability of governmental and third-party payor reimbursement for the cost of topsalysin and/or payment to the physician for administering topsalysin. In the United States, no uniform policy of coverage and reimbursement for drug products exists among third-party payors. Therefore, coverage and reimbursement for drug products can differ significantly from payor to payor. As a result, the coverage determination process is often a time-consuming and costly process that will require us to provide scientific and clinical support for the use of our products to each payor separately, with no assurance that coverage and adequate reimbursement will be obtained. One third-party payor's decision to cover a particular medical product or service does not assure that other payors will also provide coverage for the medical product or service, or to provide coverage at an adequate reimbursement rate. 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, with no assurance that adequate coverage and reimbursement will be obtained. Further, a third-party payor's decision to provide coverage for a medical product or service does not imply that an adequate reimbursement rate will be approved. The market for our product candidates will depend significantly on access to third-party payors' formularies or lists of treatments for which third-party payors provide coverage and reimbursement.

Third-party payors establish coverage and reimbursement policies for new products, including product candidates like topsalysin. In particular, in the United States, private health insurers and other third-party payors often provide reimbursement for treatments based on the level at which the government (through the Medicare or Medicaid programs) provides reimbursement for such treatments. In the United States, the EEA and other significant or potentially significant markets for our product candidate, government authorities and third-party payors are increasingly attempting to limit or regulate the price of medical products and services, particularly for new and innovative products and therapies, which has resulted in lower average selling prices. Further, the increased emphasis on managed healthcare in the United States and on country and regional pricing and reimbursement controls in Canada and the EEA will put additional pressure on product pricing, coverage, reimbursement and utilization, which may adversely affect our product sales and results of operations. These pressures can arise from policies and practices of managed care groups, judicial decisions and governmental laws and regulations related to Medicare, Medicaid and healthcare reform, coverage and reimbursement policies and pricing in general. Any reduction in reimbursement from Medicare or other government programs may result in a similar reduction in payments from private payors.

In March 2010, the Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act, or collectively, the PPACA, became law in the United States. PPACA substantially changed the way healthcare is financed by both governmental and private insurers and significantly affected the pharmaceutical industry. Among the provisions of the PPACA of greatest importance to the pharmaceutical industry are that it: (i) created an annual, nondeductible fee on any entity that manufactures or imports certain branded prescription drugs and biologic agents, apportioned among these entities according to their market share in certain government healthcare programs; (ii) increased the rebates a manufacturer must pay under the Medicaid Drug Rebate Program to 23.1% and 13% of the average manufacturer price for branded and generic drugs, respectively; (iii) created a new Medicare Part D coverage gap discount program, in which manufacturers must now agree to offer 70% point-of-sale discounts to 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; (iv) extended of manufacturers' Medicaid rebate liability to covered drugs dispensed to individuals who are enrolled in Medicaid managed care organizations; (v) expanded eligibility criteria for Medicaid programs by, among other things, allowing states to offer Medicaid coverage to additional individuals with income at or below 133% of the Federal Poverty Level, thereby potentially increasing manufacturers' Medicaid rebate liability; (vi) expanded the entities eligible for discounts under the Public Health Service pharmaceutical pricing program; (vii) expanded health care fraud and abuse laws, including the federal civil False Claims Act and the federal healthcare anti-kickback statute, new government investigative powers, and enhanced penalties for noncompliance; and (viii) created a new Patient-Centered Outcomes Research Institute to oversee, identify priorities in, and conduct comparative clinical effectiveness research, along with funding for such research.

Since its enactment there have been judicial and Congressional challenges to certain aspects of the PPACA, as well as efforts by the Trump administration to repeal or replace certain aspects of the PPACA. Since January 2017, President Trump has signed two Executive Orders and other directives designed to delay the implementation of certain provisions of the PPACA or otherwise circumvent some of the requirements for health insurance mandated by the PPACA. Concurrently, Congress has considered legislation that would repeal or repeal and replace all or part of the PPACA. While Congress has not passed comprehensive repeal legislation, two bills affecting the implementation of certain taxes under the PPACA have been signed into law. The Tax Cuts and Jobs Act of 2017, or Tax Act, included a provision which repealed, effective January 1, 2019, the tax-based shared responsibility payment imposed by the PPACA 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 PPACA-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 PPACA, effective January 1, 2019, to increase from 50 percent to 70 percent the point-of-sale discount that is owed by pharmaceutical manufacturers who participate in Medicare Part D and to close the coverage gap in most Medicare drug plans, commonly referred to as the "donut hole". In July 2018, the Centers for Medicare & Medicaid Services, or CMS, published a final rule permitting further collections and payments to and from certain PPACA qualified health plans and health insurance issuers under the PPACA 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 PPACA is unconstitutional in its entirety because the "individual mandate" was repealed by Congress as part of the Tax Cuts and Jobs Act of 2017. 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 PPACA will impact the PPACA and our business. Congress may consider other legislation to replace elements of the PPACA.

In addition, other legislative changes have been proposed and adopted in the United States since the PPACA. For example, through the process created by the Budget Control Act of 2011, there are automatic reductions of Medicare payments to providers up to 2% per fiscal year, which went into effect in April 2013 and, following passage of the BBA, will remain in effect through 2027 unless additional Congressional action is taken. 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.

Further, recently there has been heightened governmental scrutiny in the United States over the manner in which drug manufacturers set prices for their marketed products, 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. For example, 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. On January 31, 2019, the U.S. Department of Health and Human Services, Office of Inspector General, proposed modifications to the federal health care program anti-kickback statute discount safe harbor for the purpose of reducing the cost of drug products to consumers which, among other things, if finalized, will affect discounts paid by manufacturers to Medicare Part D plans, Medicaid managed care organizations and pharmacy benefit managers working with these organizations. While some of these and other proposed measures may 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 have increasingly passed legislation and implemented 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 expect that additional federal and state healthcare reform measures will be adopted in the future, any of which could result in reduced demand for our products or other adverse effects on our business.

In the EEA, the success of topsalysin, if approved, will depend largely on obtaining and maintaining government reimbursement, because in many European countries patients are unlikely to use therapies that are not reimbursed by the government. Negotiating prices with governmental authorities can delay commercialization by 12 months or more. Reimbursement policies may adversely affect our ability to sell our products on a profitable basis. In many international markets, governments control the prices of prescription pharmaceuticals, including through the implementation of reference pricing, price cuts, rebates, revenue-related taxes and profit control, and expect prices of prescription pharmaceuticals to decline over the life of the product or as volumes increase. Recently, many countries in the EEA have increased the amount of discounts required on pharmaceutical products and other therapies, and we expect these discounts to continue as countries attempt to manage healthcare expenditures, especially in light of current economic conditions. As a result of these pricing practices, it may become difficult to achieve profitability or expected rates of growth in revenue or results of operations. Any shortfalls in revenue could adversely affect our business, prospects, financial condition and results of operations.

Certain countries have a very difficult reimbursement environment and we may not obtain reimbursement or pricing approval, if required, in all countries where we expect to market a product, or we may obtain reimbursement approval at a level that would make marketing a product in certain countries not viable.

We expect to experience pricing pressures in connection with the sale of topsalysin, if approved, and any other products that we may develop, due to the trend toward managed healthcare, the increasing influence of health maintenance organizations and additional legislative proposals. If we fail to successfully secure and maintain adequate coverage and reimbursement for our products or are significantly delayed in doing so, we will have difficulty achieving market acceptance of our products and expected revenue and profitability which would have a material adverse effect on our business, prospects, financial condition and results of operations.

We are dependent on information technology systems, infrastructure and data, which exposes us to data security risks.

We are dependent upon our own or third-party information technology systems, infrastructure and data, including mobile technologies, to operate our business. The multitude and complexity of our computer systems may make them vulnerable to service interruption or destruction, disruption of data integrity, malicious intrusion, or random attacks. Likewise, data privacy or security incidents or breaches by employees or others may pose a risk that sensitive data, including our intellectual property, trade secrets or personal information of our employees, patients, customers or other business partners may be exposed to unauthorized persons or to the public. Cyber-attacks are increasing in their frequency, sophistication and intensity. Cyber-attacks could include the deployment of harmful malware, denial-of-service, social engineering and other means to affect service reliability and threaten data confidentiality, integrity and availability. Our business partners face similar risks and any security breach of their systems could adversely affect our security posture. A security breach or privacy violation that leads to disclosure or modification of or prevents access to patient information, including personally identifiable information or protected health information, could harm our reputation, compel us to comply with federal and/or state breach notification laws and foreign law equivalents, subject us to mandatory corrective action, require us to verify the correctness of database contents and otherwise subject us to litigation or other liability under laws and regulations that protect personal data, any of which could disrupt our business and/or result in increased costs or loss of revenue. Moreover, the prevalent use of mobile devices that access confidential information increases the risk of data security breaches, which could lead to the loss of confidential information, trade secrets or other intellectual property. While we have invested, and continue to invest, in the protection of our data and information technology infrastructure, there can be no assurance that our efforts will prevent service interruptions, or identify breaches in our systems, that could adversely affect our business and operations and/or result in the loss of critical or sensitive information, which could result in financial, legal, business or reputational harm to us. In addition, our liability insurance may not be sufficient in type or amount to cover us against claims related to security breaches, cyber-attacks and other related breaches.

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

Our operations could be subject to earthquakes, power shortages, telecommunications failures, systems failures, water shortages, floods, hurricanes, typhoons, fires, extreme weather conditions, medical epidemics and other natural or man-made disasters or business interruptions. The occurrence of any of these business interruptions could seriously harm our business and financial condition and increase our costs and expenses. A majority of our management operates in our principal executive offices located in San Diego, California. If our San Diego offices were affected by a natural or man-made disaster, particularly those that are characteristic of the region, such as wildfires and earthquakes, or other business interruption, our ability to manage our domestic and foreign operations could be impaired, which could materially and adversely affect our results of operations and financial condition. We currently rely, and intend to rely in the future, on our third-party manufacturers to produce our supply of topsalysin. Our ability to obtain supplies topsalysin could be disrupted, and our results of operations and financial condition could be materially and adversely affected if the operations of these third party manufacturers were affected by a man-made or natural disaster or other business interruption. The ultimate impact of such events on us, our significant suppliers and our general infrastructure is unknown.

Our business involves the use of hazardous materials, and we and our third-party manufacturers must comply with environmental laws and regulations, which can be expensive and restrict how we do business.

Our third-party manufacturers' activities involve the controlled storage, use and disposal of hazardous materials owned by us, including the components of topsalysin and other hazardous compounds. Specifically, the cleavage of the PSA-sensitive activation sequence of topsalysin in the manufacturing process could potentially lead to the release of the C-terminal inhibitory peptide resulting in the formation of active aerolysin, a pore-forming hemolytic toxin. We and our manufacturers are subject to federal, state and local as well as foreign laws and regulations governing the use, manufacture, storage, handling and disposal of these hazardous materials. Although we believe that the safety procedures utilized by our third-party manufacturers for handling and disposing of these materials comply with the standards prescribed by these laws and regulations, we cannot eliminate the risk of accidental contamination or injury from these materials. Our third-party manufacturers, do not manufacture topsalysin in its facility at the same time as it manufactures other biologics due to the toxic nature of aerolysin. In the event of an accident, state, federal or foreign authorities may curtail the use of these materials and interrupt our business operations. We do not currently maintain hazardous materials insurance coverage. If we are subject to any liability as a result of our third-party manufacturers' activities involving hazardous materials, our business and financial condition may be adversely affected. In the future we may seek to establish longer term third-party manufacturing arrangements, pursuant to which we would seek to obtain contractual indemnification protection from such third-party manufacturers potentially limiting this liability exposure.

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

We face an inherent risk of product liability as a result of the clinical testing and, if approved, the commercialization of topsalysin. For example, we may be sued if any product we develop allegedly causes injury or is 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 or foreign 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 candidate. Even a 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 or product candidates that we may develop;
- 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;
- loss of revenue;
- exhaustion of any available insurance and our capital resources;
- the inability to commercialize our products or product candidates; and
- a decline in our share price.

Our inability to obtain and retain sufficient product liability insurance at an acceptable cost to protect against potential product liability claims could prevent or inhibit the commercialization of products we develop. We currently carry product liability insurance covering our clinical studies and commercial product sales in the amount of $10 million in the aggregate.

Although we maintain such insurance, any claim that may be brought against us could result in a court judgment or settlement in an amount that is not covered, in whole or in part, by our insurance or that is in excess of the limits of our insurance coverage. If we determine that it is prudent to increase our product liability coverage due to the commercial launch of any product, we may be unable to obtain such increased coverage on acceptable terms or at all. Our insurance policies also have various exclusions, and we may be subject to a product liability claim for which we have no coverage. We will 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.

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 pharmaceuticals industries depends upon our ability to attract and retain highly qualified managerial, scientific and medical personnel. We are highly dependent on our management and scientific and medical personnel, including our Chief Executive Officer and President, Randall E. Woods and our Chief Operating Officer and Head of Research and Development, Allison Hulme Ph.D. and multiple outside consultants. In order to retain valuable employees at our company, in addition to salary and cash incentives, we provide incentive stock options that vest over time. The value to employees of stock options that vest over time will be significantly affected by movements in our share price that are beyond our control and may at any time be insufficient to counteract more lucrative offers from other companies.

Our scientific team in particular has expertise in many different aspects of drug development and may be difficult to retain or replace. We conduct our operations at our facilities in San Diego, California and this region is headquarters to many other biopharmaceutical companies and many academic and research institutions and therefore we face increased competition for personnel in this location. Competition for skilled personnel in our market is very intense and competition for experienced scientists may limit our ability to hire and retain highly qualified personnel on acceptable terms.

In addition, we have scientific and clinical advisors who assist us in formulating our product development and clinical strategies. These advisors are not our employees and may have commitments to, or consulting or advisory contracts with, other entities that may limit their availability to us, or may have arrangements with other companies to assist in the development of products that may compete with ours.

Despite our efforts to retain valuable employees, members of our management and scientific and development teams may terminate their employment with us on short notice. Although we have written employment arrangements with all of our employees, these employment arrangements provide for at-will employment, which means that our employees can leave our employment at any time, with or without notice. The loss of the services of any of our executive officers or other key employees and our inability to find suitable replacements could potentially harm our business, financial condition and prospects. We do not maintain "key man" insurance policies on the lives of these individuals or the lives of any of our other employees.

Our employees, independent contractors, consultants, commercial partners and vendors may engage in misconduct or other improper activities, including noncompliance with regulatory standards and requirements and insider trading.

We are exposed to the risk of fraud or other illegal activity by our employees, independent contractors, consultants, 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 regulatory bodies; provide true, complete and accurate information to the FDA and other similar regulatory bodies; comply with manufacturing standards we have established; comply with federal and state healthcare fraud and abuse and health regulatory laws and other similar foreign fraudulent misconduct laws; or report financial information or data accurately or disclose unauthorized activities to us. These laws may impact, among other things, our activities with principal investigators and research subjects, as well as our sales, marketing and education programs. In particular, the promotion, sales, and marketing of health care items and services, as well as certain business arrangements in the healthcare industry, are subject to extensive laws intended to prevent fraud, misconduct, kickbacks, self-dealing and other abusive practices. These laws may restrict or prohibit a wide range of pricing, discounting, marketing and promotion, structuring and commission(s), certain customer incentive programs and other business arrangements generally. Misconduct could also involve the improper use or disclosure of information obtained in the course of clinical trials, which could result in regulatory sanctions and serious harm to our reputation. Additionally, we are subject to state and foreign equivalents of each of the healthcare laws described above, some of which may be broader in scope and may apply regardless of the payor.

We have adopted a Code of Business Conduct and Ethics, but it is not always possible to identify and deter 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. Efforts to ensure that our business arrangements will comply with applicable healthcare laws may 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. 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 significant civil, criminal and administrative penalties, damages, monetary fines, disgorgement, imprisonment, possible exclusion from participation in Medicare, Medicaid and other federal healthcare programs, 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, contractual damages, reputational harm, diminished profits and future earnings, and curtailment of our operations, any of which could adversely affect our ability to operate our business and our results of operations. Defending against any such actions can be costly, time-consuming and may require significant financial and personnel resources. Therefore, even if we are successful in defending against any such actions that may be brought against us, our business may be impaired.

If we are unable to establish sales and marketing capabilities or enter into agreements with third parties to market and sell any products we may develop, we may not be able to effectively market and sell our products and generate product revenue.

We are developing topsalysin for large patient populations served by urologists and oncologists as well as general practice physicians, which number in the tens of thousands in the United States. Traditional pharmaceutical companies employ groups of sales representatives numbering in the thousands to call on this large of a number of physicians. We do not currently have an organization for the sale, marketing or distribution of topsalysin and we must build this organization or make arrangements with third parties to perform these functions in order to commercialize topsalysin and any future products. We intend to establish (either internally or through a contract sales force) a sales force to sell topsalysin, if approved, in the United States, although any partnership that we establish for the development of topsalysin will likely provide U.S. commercialization rights or co-commercialization rights to the partner for this indication. We plan to partner with third parties to commercialize topsalysin outside the United States. The establishment and development of our own sales force or the establishment of a contract sales force to market any products we may develop in the United States will be expensive and time consuming and could delay any product launch, and we cannot be certain that we would be able to successfully develop this capacity. If we are unable to establish our sales and marketing capability or any other non-technical capabilities necessary to commercialize any products we may develop, we will need to contract with third parties to market and sell such products in the United States. We currently possess limited resources and may not be successful in establishing our own internal sales force or in establishing arrangements with third parties on acceptable terms, if at all.

Changes in funding for the FDA, the SEC and other government agencies could hinder their ability to hire and retain key leadership and other personnel, prevent new products and services from being developed or commercialized in a timely manner or otherwise prevent those agencies from performing normal functions on which the operation of our business may rely, which could negatively impact our business.

The ability of the FDA to review and approve new products can be affected by a variety of factors, including government budget and funding levels, ability to hire and retain key personnel and accept payment of user fees, and statutory, regulatory, and policy changes. Average review times at the agency have fluctuated in recent years as a result. In addition, government funding of the SEC and other government agencies on which our operations may rely, including those that fund research and development activities is subject to the political process, which is inherently fluid and unpredictable.

Disruptions at the FDA and other agencies may also slow the time necessary for new drugs to be reviewed and/or approved by necessary government agencies, which would adversely affect our business. For example, over the last several years, including beginning on December 22, 2018, the U.S. government has shut down several times and certain regulatory agencies, such as the FDA and the SEC, have had to furlough critical FDA, SEC and other government employees and stop critical activities. If a prolonged government shutdown occurs, it could significantly impact the ability of the FDA to timely review and process our regulatory submissions, which could have a material adverse effect on our business. Further, future government shutdowns could impact our ability to access the public markets and obtain necessary capital in order to properly capitalize and continue our operations.

Risks Related to our Financial Position and Capital Requirements

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

We have a limited operating history and we have financed our operations primarily through equity and debt financings and have incurred significant operating losses since our inception. We had a net loss of $6.8 million, $8.6 million, and $11.2 million during the years ended December 31, 2018, 2017 and 2016, respectively. As of December 31, 2018, we had an accumulated deficit of $156.3 million. Our prior losses, combined with expected future losses, have had and will continue to have an adverse effect on our shareholders' equity and working capital. Our losses have resulted principally from costs incurred in our research activities for topsalysin. We anticipate that our operating losses will substantially increase over the next several years as we continue development of topsalysin, including the conduct of any future clinical trials for the treatment of clinically significant localized prostate cancer and as a treatment for the lower urinary tract symptoms of BPH. In addition, if we obtain regulatory approval of topsalysin in either indication, we may incur significant sales and marketing expenses and outsourced manufacturing expenses, as well as continued development expenses. Because of the numerous risks and uncertainties associated with developing pharmaceutical products, we are unable to predict the extent of any future losses or whether or when we will become profitable.

We have not generated any product revenue and may never become profitable.

Our ability to become profitable depends upon our ability to develop and commercialize topsalysin. To date, other than the upfront payment we received from Kissei and the $5.0 million milestone payment we received in April 2013 from Kissei for the achievement of a development milestone, we have not generated any revenue from topsalysin and we do not know when, or if, we will generate any future revenue. Our ability to generate future revenue depends on a number of factors, including:

- successfully completing the clinical development topsalysin in one or both indications;
- obtaining U.S. and/or foreign regulatory approvals for topsalysin in one or both indications;
- manufacturing commercial quantities of topsalysin at acceptable costs levels if regulatory approvals are received;
- achieving broad market acceptance of topsalysin in the medical community and with third-party payors and patients; and
- creating an internal commercial infrastructure or identifying and entering into one or more strategic collaborations to effectively market and sell topsalysin.

We may never be able to successfully develop or commercialize topsalysin in either indication. Even if we do obtain regulatory approval to commercialize topsalysin, which we do not expect to occur for several years, we may never generate product sales and may never achieve or sustain profitability on a quarterly or annual basis. Our failure to become and remain profitable would depress the market price of our common shares and could impair our ability to raise capital, expand our business, diversify our product offerings or continue our operations.

Raising additional capital may cause dilution to our existing shareholders, restrict our operations or require us to relinquish intellectual property rights to our product candidates.

We may seek additional capital through a combination of public and private equity offerings, debt financings, strategic partnerships and alliances and licensing arrangements. To the extent that we raise additional capital through the sale of equity or convertible debt securities, the ownership interest of our existing shareholders will be diluted, and the terms may include liquidation or other preferences that adversely affect the rights of our shareholders. Debt financings may be coupled with an equity component, such as warrants to purchase shares, which could also result in dilution of our existing shareholders' ownership. The incurrence of indebtedness would result in increased fixed payment obligations and could also result in certain restrictive covenants, such as limitations on our ability to incur additional debt, limitations on our ability to acquire or license intellectual property rights and other operating restrictions that could adversely impact our ability to conduct our business. If we raise additional funds through strategic partnerships and alliances and licensing arrangements with third parties, we may have to relinquish valuable rights to our product candidates, or grant licenses on terms that are not favorable to us.

The recently passed comprehensive tax reform bill could adversely affect our business and financial condition.

On December 22, 2017, the president of the United States signed into law the Tax Act that significantly revises the Internal Revenue Code of 1986, as amended. The newly enacted federal income tax law, among other things, contains 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 modifying or repealing many business deductions and credits. Notwithstanding the reduction in the corporate income tax rate, the overall impact of the new federal tax law is uncertain and our business and financial condition could be adversely affected. In addition, it is uncertain if and to what extent various states will conform to the newly enacted federal tax law.

Fluctuations in foreign currency exchange rates could result in changes in our reported revenues and earnings.

We currently incur expenses denominated in foreign currencies for multiple vendors. This includes our manufacturing and supply agreements for the manufacture of topsalysin, for which payments are denominated in foreign currency. In addition, we are utilizing several clinical vendors which are located in various countries outside of the United States. These clinical vendors invoice us in the local currency of the vendor. We do not engage in foreign currency hedging arrangements for our accounts payable, and, consequently, foreign currency fluctuations may adversely affect our earnings. During the years ended December 31, 2018 and 2017, 41.9% and 18.1% respectively, of our operating expenses were denominated in currencies other than the U.S. dollar. Going forward we anticipate that our sales and expenses, if any, will be denominated in the local currency of the country in which they occur. We may decide to manage this risk by hedging our foreign currency exposure, principally through derivative contracts. Even if we decide to enter into such hedging transactions, we cannot be sure that such hedges will be effective or that the costs of such hedges will not exceed their benefits. Fluctuations in the rate of exchange between the U.S. dollar and foreign currencies, primarily the euro, could result in material amounts of cash being required to settle the hedge transactions or could adversely affect our financial results.

Risks Related to our Intellectual Property

If we are unable to obtain or protect intellectual property rights related to our product candidates, we may not be able to compete effectively in our market.

We rely upon a combination of patents, trade secret protection and confidentiality agreements to protect the intellectual property related to our product candidates. The strength of patents in the biotechnology and pharmaceutical field involves complex legal and scientific questions and can be uncertain. The patent applications that we own or in-license may fail to result in issued patents with claims that cover the products in Canada, the United States or in other foreign countries. If this were to occur, early generic competition could be expected against product candidates in development. There is no assurance that all of the potentially relevant prior art relating to our patents and patent applications has been found, which can invalidate a patent or prevent a patent from issuing based on a pending patent application. Even if patents do successfully issue, third parties may challenge their validity, enforceability or scope, which may result in such patents being narrowed or invalidated.

Composition-of-matter patents on the biological or chemical active pharmaceutical ingredient are generally considered to be the strongest form of intellectual property protection for pharmaceutical products, as such patents provide protection without regard to any method of use. We cannot be certain that the claims in our patent applications covering composition-of-matter of topsalysin will be considered patentable by the U.S. Patent and Trademark Office, or U.S. PTO, and courts in the United States or by the patent offices and courts in foreign countries. Method-of-use patents protect the use of a product for the specified method. This type of patent does not prevent a competitor from making and marketing a product that is identical to our product for an indication that is outside the scope of the patented method. Moreover, even if competitors do not actively promote their product for our targeted indications, physicians may prescribe these products off-label. Although off-label prescriptions may infringe or contribute to the infringement of method-of-use patents, the practice is common and such infringement is difficult to prevent or prosecute. Furthermore, even if they are unchallenged, our patents and patent applications may not adequately protect our intellectual property or prevent others from designing around our claims. If the patent applications we hold with respect to topsalysin fail to issue or if their breadth or strength of protection is threatened, it could dissuade companies from collaborating with us to develop them, and threaten our ability to commercialize, our products. We cannot offer any assurances about which, if any, patents will issue or whether any issued patents will be found not invalid and not unenforceable or will go unthreatened by third parties. Further, if we encounter delays in regulatory approvals, the period of time during which we could market topsalysin under patent protection could be reduced. Since patent applications in the United States and most other countries are confidential for a period of time after filing, and some remain so until issued, we cannot be certain that we were the first to file any patent application related to topsalysin. Furthermore, if third parties have filed such patent applications, an interference proceeding in the United States can be provoked by a third party or instituted by us to determine who was the first to invent any of the subject matter covered by the patent claims of our applications.

In addition to the protection afforded by patents, we rely on trade secret protection and confidentiality agreements to protect proprietary know-how that is not patentable, processes for which patents are difficult to enforce and any other elements of our drug discovery and development processes that involve proprietary know-how, information or technology that is not covered by patents. Although we expect all of our employees to assign their inventions to us, and all of our employees, consultants, advisors and any third parties who have access to our proprietary know-how, information or technology to enter into confidentiality agreements, we cannot provide any assurances that all such agreements have been duly executed or that our trade secrets and other confidential proprietary information will not be disclosed or that competitors will not otherwise gain access to our trade secrets or independently develop substantially equivalent information and techniques.

The Leahy-Smith America Invents Act, or the Leahy-Smith Act, was signed into law in September 2011 and includes a number of significant changes to U.S. patent law. These include changes in the way patent applications will be prosecuted and may also affect patent litigation. The U.S. PTO is currently developing regulations and procedures to administer the Leahy-Smith Act, and many of the substantive changes to patent law associated with the Leahy-Smith Act will not become effective until one year or 18 months after its enactment. Accordingly, it is not clear what, if any, impact the Leahy-Smith Act will have on the cost of prosecuting our patent applications, our ability to obtain patents based on our patent applications and our ability to enforce or defend our issued patents. An inability to obtain, enforce and defend patents covering our proprietary technologies would materially and adversely affect our business prospects and financial condition. Further, the laws of some foreign countries do not protect proprietary rights to the same extent or in the same manner as the laws of the United States and Canada. As a result, we may encounter significant problems in protecting and defending our intellectual property both in the United States and abroad. If we are unable to prevent material disclosure of the non-patented intellectual property related to our technologies to third parties, and there is no guarantee that we will have any such enforceable trade secret protection, we may not be able to establish or maintain a competitive advantage in our market, which could materially adversely affect our business, results of operations and financial condition.

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 party reexamination proceedings before the U.S. PTO. Numerous U.S. and foreign issued patents and pending patent applications, which are owned by third parties, exist in the fields in which we, and our collaborators, are developing product 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 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 topsalysin. 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. We are aware of at least one third-party patent that may be relevant to our product candidates. If any third-party patents were held by a court of competent jurisdiction to cover the manufacturing process of any of our product candidates, any molecules formed during the manufacturing process 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 patent 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 patent 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, would 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, obtain one or more licenses from third parties, pay royalties or redesign our infringing products, which may be impossible or require substantial time and monetary expenditure. We cannot predict whether any such license would be available at all or whether it would be available on commercially reasonable terms. Furthermore, even in the absence of litigation, 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 would be unable to further develop and commercialize one or more of our 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 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.

If we fail to comply with our obligations in the agreements under which we license rights to technology from third parties, we could lose license rights that are important to our business.

We are a party to a number of technology license agreements that are essential to our business and expect to enter into additional license agreements in the future. For example, we have exclusive licenses to topsalysin from UVIC Industry Partnerships Inc. and The Johns Hopkins University. The agreements governing these exclusive licenses include provisions that permit the licensors to terminate the license agreements in a number of situations, including if we grant a security interest on the licensed technology. These licensors might claim that filings made by Oxford Finance LLC, or Oxford, with the U.S. PTO or foreign jurisdictions in 2011 in connection with our Oxford Loan and Security Agreement imposed a security interest on the applicable technology. However, no claims from these licensors have been made to date regarding violations of these license agreements as a result of these filings and these filings were released when we repaid the outstanding balance under the Oxford Loan and Security Agreement in full in 2016. Furthermore, if any such claims are made in the future, we believe that such claims would not have merit and we would vigorously defend and reject such claims. If we fail to comply with our obligations under our license agreements, or we are insolvent or subject to a bankruptcy proceeding, the applicable licensor may have the right to terminate such license agreement, in which event we would not be able to market products covered by such license agreement, including topsalysin. We may also be subjected to litigation or other potential disputes under our license agreements if we fail to comply with our obligations under those agreements. The loss of our rights to technology that we have licensed under certain agreements would have a material adverse effect on our business.

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 or is unenforceable, 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 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 collaborators or 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 or interference 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 shares.

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 on any issued patent are due to be paid to the U.S. PTO and foreign patent agencies in several stages over the lifetime of the patent. The U.S. PTO and various foreign governmental patent agencies require compliance with a number of procedural, documentary, fee payment and other similar provisions during the patent application process. While an inadvertent lapse can in many cases be cured by payment of a late fee or by other means in accordance with the applicable rules, there are situations in which noncompliance 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. Non-compliance events that could result in abandonment or lapse of a patent or patent application include, but are not limited to, failure to respond to official actions within prescribed time limits, non-payment of fees and failure to properly legalize and submit formal documents. If we or our licensors fail to maintain the patents and patent applications covering our product candidates, our competitors might be able to enter the market, which would have a material adverse effect 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.

We employ individuals who were previously employed at other biotechnology or pharmaceutical companies. We may be subject to claims that we or our employees, consultants or independent contractors have inadvertently or otherwise used or disclosed confidential information of our employees' former employers or other third parties. We may also be subject to claims that former employers or other third parties have an ownership interest in our patents. Litigation may be necessary to defend against these claims. There is no guarantee of success in defending these claims, and if we are successful, litigation could result in substantial cost and be a distraction to our management and other employees.

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, including China, 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 product candidates 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 and other intellectual property protection, particularly those relating to biopharmaceuticals, 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 Shares

If we fail to satisfy applicable listing standards, our common shares may be delisted from The Nasdaq Capital Market.

On March 7, 2019, we received a letter (the "Notice") from the Listing Qualifications Staff of The Nasdaq Stock Market LLC ("Nasdaq") notifying us that for the last 30 consecutive business days prior to the date of the Notice, the market value of our listed securities was less than $35 million and therefore we did not meet the requirement for continued listing on The Nasdaq Capital Market as required by Nasdaq Listing Rule 5550(b)(2) (the "Market Value Rule") or the alternative requirements under Nasdaq Listing Rules 5550(b)(1) and 5550(b)(3). In accordance with Nasdaq Listing Rule 5810(c)(3)(C), we have 180 calendar days, or until September 3, 2019, to regain compliance with the Market Value Rule. We will regain compliance with the Market Value Rule if the market value of our listed securities closes at or above $35 million for a minimum of 10 consecutive business days anytime during the 180 day compliance period.

There is no guarantee that we will be able to regain compliance with the Nasdaq Market Value Rule, which could result in Nasdaq taking steps to delist our common shares. Delisting from The Nasdaq Capital Market could adversely affect our ability to raise additional financing through the public or private sale of equity securities, would significantly affect the ability of investors to trade our securities and would negatively affect the value and liquidity of our common shares. Delisting could also have other negative results, including the potential loss of confidence by employees, the loss of institutional investor interest and fewer business development opportunities. If our common shares are delisted by The Nasdaq Capital Market, the price of our common shares may decline, and although our common shares may be eligible to trade on the OTC Bulletin Board, another over-the-counter quotation system, or on the pink sheets, an investor may find it more difficult to dispose of their common shares or obtain accurate quotations as to the market value of our common shares. Further, if we are delisted, we would incur additional costs under state blue sky laws in connection with any sales of our securities. These requirements could severely limit the market liquidity of our common shares and the ability of our shareholders to sell our common shares in the secondary market.

U.S. holders of our shares may suffer adverse tax consequences if we are characterized as a passive foreign investment company after 2012.

Generally, if for any taxable year 75% or more of our gross income is passive income, or at least 50% of the average quarterly value of our assets (which may be determined in part by the market value of our ordinary shares, which is subject to change) are held for the production of, or produce, passive income, we would be characterized as a passive foreign investment company, or PFIC, for United States federal income tax purposes. Based on the composition of our gross income and gross assets and the nature of our business, we expect that we were a PFIC for the taxable years ending December 31, 2012 through 2017 and that we will likely be a PFIC for the taxable year ending December 31, 2018. In 2018 and for future years, our status as a passive foreign investment company will also depend on whether we are a "controlled foreign corporation" for U.S. federal income tax purposes, how quickly we utilize the cash proceeds from our initial public offering, or IPO, in our business and other factors. If we are a PFIC for the taxable year ending December 31, 2018 or any subsequent year, U.S. holders of our shares may suffer adverse tax consequences. Gains realized by non-corporate U.S. holders on the sale of our ordinary shares would be taxed as ordinary income, rather than as capital gain, and the preferential tax rate applicable to dividends received on our ordinary shares would be lost. Interest charges would also be added to taxes on gains and dividends realized by all U.S. holders.

A U.S. holder may avoid these adverse tax consequences by timely making a qualified electing fund election. For each year that we would meet the PFIC gross income or asset test, an electing U.S. holder would be required to include in gross income its pro rata share of our net ordinary income and net capital gains, if any. A U.S. holder may make a qualified electing fund election only if we commit to provide U.S. holders with their pro rata share of our net ordinary income and net capital gains. Because we intend to provide this information, a U.S. holder should be eligible to make a qualified electing fund election.

A U.S. holder may also mitigate the adverse tax consequences of being a PFIC by timely making a mark-to-market election. Generally, for each year that we would meet the PFIC gross income or asset test, an electing U.S. holder would include in gross income the increase in the value of its shares during each of its taxable years and deduct from gross income the decrease in the value of such shares during each of its taxable years. A mark-to-market election may be made and maintained only if our shares are regularly traded on a qualified exchange. While we anticipate that these requirements were satisfied following our IPO, whether our shares are regularly traded on a qualified exchange is an annual determination based on facts that, in part, are beyond our control. Accordingly, we can provide no assurances that a U.S. holder will be eligible to make a mark-to-market election. You should consult your own tax advisor as to the specific tax consequences to you in the event we are characterized as a PFIC for the taxable year ending December 31, 2018 or any subsequent year.

The financial reporting obligations of being a public company require significant company resources and management attention.

We are subject to the public company reporting obligations under the Exchange Act and the rules and regulations regarding corporate governance practices, including those under the Sarbanes-Oxley Act of 2002, or the Sarbanes-Oxley Act, the Dodd-Frank Wall Street Reform and Consumer Protection Act, or the Dodd-Frank Act, and the listing requirements of The Nasdaq Capital Market. As a result, we have incurred, and will continue to incur, significant legal, accounting and other expenses, particularly now that we are no longer an "emerging growth company" as defined in the JOBS Act. Further, the need to establish the corporate infrastructure demanded of a public company may divert management's attention from implementing our growth strategy. We have made, and will continue to make, changes to our corporate governance standards, disclosure controls and financial reporting and accounting systems to meet our reporting obligations. Any changes that we make to comply with these obligations may not be sufficient to allow us to satisfy our obligations as a public company on a timely basis, or at all, which could subject us to delisting of our common shares, fines, sanctions and other regulatory action and potentially civil litigation. In addition, we incur significant legal, accounting, reporting and other expenses in order to maintain a listing on The Nasdaq Capital Market. These expenses relate to, among other things, the obligation to present financial information according to U.S. GAAP in the United States. We are also required to comply with certain disclosure and filing requirements under applicable securities laws in Canada as a reporting issuer in certain provinces.

The price of our common shares is likely to be highly volatile, and you could lose all or part of your investment.

The trading price of our common shares has been volatile and is likely to continue to be volatile and could be subject to wide fluctuations in response to various factors, some of which are beyond our control, including limited trading volume. In addition to the other risk factors discussed in this section, these factors include:

- the outcome of our pursuit of strategic alternatives, including whether we raise any additional capital to fund our ongoing operations;
- the results of our completed and future clinical trials of topsalysin or changes in the development status of topsalysin;
- any adverse development or perceived adverse development with respect to our submission of a BLA to the FDA for topsalysin;
- unanticipated serious safety concerns related to the use of topsalysin;
- adverse regulatory decisions, including failure to receive regulatory approval for topsalysin;
- our decision to initiate a clinical trial, not to initiate a clinical trial or to terminate an existing clinical trial;
- our ability to obtain resources for us and our clinical trial programs on our desired schedule;
- inability to obtain adequate commercial supply for any approved product or inability to do so at acceptable prices;
- changes in the structure of healthcare payment systems;
- developments concerning our commercial partners, including but not limited to, those with manufacturers;
- competition from existing technologies and products or new technologies and products that may emerge;
- announcements of significant acquisitions, strategic partnerships, joint ventures, new products, capital commitments or other events by us or our competitors;
- the inability to establish collaborations or termination of a collaboration;
- actual or anticipated variations in our quarterly operating results;

- failure to meet the estimates and projections of the investment community or that we may otherwise provide to the public;
- our cash position;
- announcement or expectation of additional financing efforts;
- issuances of debt or equity securities;
- our inability to successfully enter new markets or develop additional product candidates;
- actual or anticipated fluctuations in our competitors' operating results or changes in their growth rate;
- sales of our common shares by us, or our shareholders in the future;
- trading volume of our common shares on The Nasdaq Capital Market and price;
- market conditions in our industry;
- overall performance of the equity markets and general political and economic conditions;
- introduction of new products or services by us or our competitors;
- additions or departures of key management, scientific or other personnel;
- publication of research reports about us or our industry or positive or negative recommendations or withdrawal of research coverage by securities or industry analysts;
- changes in the market valuation of similar companies;
- disputes or other developments related to intellectual property and other proprietary rights, including patents, litigation matters and our ability to obtain patent protection for our technologies and product candidates;
- changes in laws or regulations and policies applicable to product candidates, including but not limited to clinical trial requirements for approvals;
- changes in accounting practices;
- significant lawsuits, including patent or shareholder litigation; and
- other events or factors, many of which are beyond our control.

Furthermore, the stock markets have experienced extreme price and volume fluctuations that have affected and continue to affect the market prices of equity securities of many companies. These fluctuations often have been unrelated or disproportionate to the operating performance of those companies. These broad market and industry fluctuations, as well as general economic, political and market conditions such as recessions, interest rate changes or international currency fluctuations, may negatively impact the market price of our common shares.

Future sales and issuances of our common shares or rights to purchase common shares by us, including pursuant to our equity incentive plan, could result in additional dilution of the percentage ownership of our shareholders and could cause our share price to fall.

We expect that significant additional capital will be needed in the future to continue our planned operations, including commercialization efforts, expanded research and development activities and costs associated with operating as a public company. To the extent we raise additional capital by issuing equity or convertible securities, our shareholders may experience substantial dilution. We may sell common shares, 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 shares, convertible securities or other equity securities in more than one transaction, investors may be materially diluted by subsequent sales. Such sales may also result in material dilution to our existing shareholders, and new investors could gain rights superior to our existing shareholders.

Pursuant to our equity incentive plan, our management is authorized to grant options to our employees, directors and consultants. The number of shares available for future grant under our plan is equal to 10% of all shares of our issued and outstanding common shares at any time. Currently, the number of shares available for issuance under our equity incentive plan automatically increases when we issue additional common shares. If our board of directors elects to grant additional options each year our shareholders may experience additional dilution, which could cause our share price to fall.

We are at risk of securities class action litigation.

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

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

We have never declared or paid any cash dividend on our common shares. 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. Our Loan and Security Agreement with SVB also contains a negative covenant which prohibits us from paying dividends without the prior written consent of SVB. Any return to shareholders will therefore be limited to the increase, if any, of our share price.

Our charter documents, certain related party contracts and certain Canadian legislation could delay or deter a change of control, limit attempts by our shareholders to replace or remove our current management and limit the market price of our common shares.

Our authorized preferred shares are available for issuance from time to time at the discretion of our board of directors, without shareholder approval. Our articles grant our board of directors the authority, subject to the BCBCA, to determine the special rights and restrictions granted to or imposed on any unissued series of preferred shares, and those rights may be superior to those of our common shares.

In addition, provisions in the BCBCA and in our articles, may have the effect of delaying or preventing changes in our management, including provisions that:

- prohibit cumulative voting in the election of directors; and
- require the approval of our board of directors or the holders of a supermajority of our outstanding share capital to amend our articles and our notice of articles.

These provisions may frustrate or prevent any attempts by our shareholders to replace or remove our current management by making it more difficult for shareholders to replace members of our board of directors, which is responsible for appointing the members of our management. Any of the foregoing could prevent or delay a change of control and may deprive or limit strategic opportunities to our shareholders to sell their shares.

Risks Related To Being A Canadian Entity

We are governed by the corporate laws in British Columbia, Canada which in some cases have a different effect on shareholders than the corporate laws in Delaware, United States.

The material differences between the BCBCA as compared to the Delaware General Corporation Law, or the DGCL, which may be of most interest to shareholders include the following: (i) for material corporate transactions (such as mergers and amalgamations, other extraordinary corporate transactions, amendments to our articles) the BCBCA generally requires two-thirds majority vote by shareholders, whereas DGCL generally only requires a majority vote of shareholders for similar material corporate transactions; (ii) the quorum for shareholders meetings is not prescribed under the BCBCA and is only two persons representing 5% of the issued shares under our articles, whereas under DGCL, quorum requires a minimum of one-third of the shares entitled to vote to be present and companies' certificates of incorporation frequently require a higher percentage to be present; (iii) under the BCBCA a holder of 5% or more of our common shares can requisition a special meeting at which any matters that can be voted on at our annual meeting can be considered, whereas the DGCL does not give this right; (iv) our articles require two-thirds majority vote by shareholders to pass a resolution for one or more directors to be removed, whereas DGCL only requires the affirmative vote of a majority of the shareholders; however, many public company charters limit removal of directors to a removal for cause; and (v) our articles may be amended by resolution of our directors to alter our authorized share structure, including to (a) consolidate or subdivide any of our shares and (b) create additional classes or series of shares, whereas under DGCL, a majority vote by shareholders is generally required to amend a corporation's certificate of incorporation and a separate class vote may be required to authorize alterations to a corporation's authorized share structure. We cannot predict if investors will find our common shares less attractive because of these material differences. If some investors find our common shares less attractive as a result, there may be a less active trading market for our common shares and our share price may be more volatile.

Item 1B. Unresolved Staff Comments

None.

Item 2. Properties

Our corporate headquarters are located in San Diego, California. The facility we lease encompasses approximately 2,002 square feet of office space. The lease for this facility expires in May 2020. We believe that our facility is sufficient to meet our needs and that suitable additional space will be available as and when needed.

Item 3. Legal Proceedings

We are not currently party to any material legal proceedings.

Item 4. Mine Safety Disclosures

None.

Part II.

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

Market Information

Our common shares are currently traded on The Nasdaq Capital Market under the symbol "SPHS."

The following table sets forth the high and low sales prices for our common shares for the period January 1, 2017 through December 31, 2018.

2017	**High**	**Low**
First Quarter	$ 3.24	$ 2.33
Second Quarter	2.85	1.83
Third Quarter	2.36	1.80
Fourth Quarter	2.57	1.80
2018		
First Quarter	$ 2.49	$ 1.90
Second Quarter	4.05	1.85
Third Quarter	3.49	2.35
Fourth Quarter	2.87	0.75

Holders of Record

As of February 13, 2019, there were approximately 10 shareholders of record of our common shares, which included Cede & Co., a nominee for Depository Trust Company, or DTC, and CDS & Co., a nominee for The Canadian Depository for Securities Ltd., or CDS. Common shares that are held by financial institutions as nominees for beneficial owners are deposited into participant accounts at either DTC or CDS and are considered to be held of record by Cede & Co. or CDS & Co. as one shareholder.

Repurchases of Equity Securities

There were no repurchases of equity securities during the fourth quarter of 2018.

Item 6. Selected Financial Data

Under SEC rules and regulations, as a smaller reporting company, we are not required to provide the information required by this item.

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

You should read the following discussion and analysis in conjunction with "Item 8. Financial Statements and Supplementary Data" included below in this Annual Report on Form 10-K. Operating results are not necessarily indicative of results that may occur in future periods.

This discussion and analysis contains forward-looking statements that involve a number of risks, uncertainties and assumptions. Actual events or results may differ materially from our expectations. Important factors that could cause actual results to differ materially from those stated or implied by our forward-looking statements include, but are not limited to, those set forth in "Item 1A. Risk Factors" in this Annual Report on Form 10-K. All forward-looking statements included in this Annual Report on Form 10-K are based on information available to us as of the time we file this Annual Report on Form 10-K and, except as required by law, we undertake no obligation to update publicly or revise any forward-looking statements.

All dollar amounts are expressed in U.S. dollars unless otherwise noted. All amounts converted from Canadian dollars to U.S. dollars are calculated using the conversion rate as of December 31, 2018 unless otherwise noted.

Overview

Background

We are a clinical-stage biopharmaceutical company focused on developing innovative products for the treatment of urological diseases. We are headquartered in San Diego, California and our common shares currently trade on The Nasdaq Capital Market. We are currently developing topsalysin (PRX302) as a treatment for clinically significant localized prostate cancer and as a treatment for the lower urinary tract symptoms of benign prostatic hyperplasia, or BPH, commonly referred to as an enlarged prostate. Topsalysin, a first-in-class, pore-forming protein, is a highly ablative agent that is selective and targeted in that it is only activated by enzymatically active prostate specific antigen, or PSA, which is found in high concentrations around prostate tumor cells and in the transition zone of the prostate. In 2004, we licensed exclusive rights to topsalysin from UVIC Industry Partnerships Inc., or UVIC, and The Johns Hopkins University, or Johns Hopkins, for the treatment of prostate cancer and in 2009, we licensed exclusive rights to topsalysin from UVIC and Johns Hopkins for the treatment of the symptoms of BPH. In April 2010, we entered into an exclusive license agreement with Kissei Pharmaceuticals Co., Ltd., or Kissei, pursuant to which we granted Kissei the right to develop and commercialize topsalysin in Japan for the treatment of the symptoms of BPH, prostate cancer, prostatitis or other diseases of the prostate.

Topsalysin, a genetically modified recombinant protein, is delivered via ultrasound-guided injection directly into the prostate. This membrane-disrupting protein is selectively activated by enzymatically active PSA, which is found in high concentrations around prostate tumor cells and in the transition zone of the prostate, leading to localized cell death and tissue disruption without damage to neighboring tissue and nerves. This targeted method of administration limits the potential for systemic exposure of topsalysin, together with the specific mechanism of action, (topsalysin, is only activated by enzymatically active PSA which is found within the prostate, PSA in circulation is no longer enzymatically active) is thought to contribute the tolerability and safety profile observed to date.

We have recently completed a multicenter, open-label Phase 2b clinical trial to confirm the dose and optimize the delivery of topsalysin for the treatment of clinically significant localized prostate cancer. The study utilized commercially available software to co-register previously obtained multi-parametric magnetic resonance imaging, or mpMRI, images of a patient's prostate to a real time 3D ultrasound to target the delivery of topsalysin directly into and around a pre-identified clinically significant tumor. A clinically significant tumor that warranted treatment was defined as, either a Gleason score 6 (pattern 3+3) and greater than or equal to 6 mm up to 10 mm, Maximum Cancer Core Length, or MCCL, or a Gleason score 7 (pattern 3+4 or 4+3) and lesser than or equal to 10 mm MCCL. The Gleason grading system is used to provide a prognosis of the identified cancer by assigning a Gleason Score and pattern. A high Gleason score indicates aggressive cancer, with a Gleason Score 6 generally representing low risk disease, Gleason 7 intermediate risk and Gleason 8-10 high risk disease.

The primary objective of the trial was to evaluate the safety and tolerability of a single administration of topsalysin, when used to focally ablate a histologically-proven, clinically significant lesion in patients with low-to-intermediate localized prostate cancer.

A total of 38 patients with a pre-identified clinically significant lesion, received a single administration of topsalysin at eight clinical trial sites located in the United Kingdom and United States. A review of the safety data from 38 patients, indicates that a single administration of topsalysin continues to appear safe and well-tolerated by patients. Adverse events considered related to topsalysin were typically mild and typically occurred and were resolved on the day of the administration. In addition, urine function was preserved, no sexual dysfunction, no hypersensitivity reactions or other serious systemic reactions to topsalysin were observed after a single administration.

A secondary objective of the trial was to evaluate the efficacy of a single administration of topsalysin to selectively target and focally ablate a pre-identified lesion. Six months after the administration of topsalysin, 37 out of 38 patients underwent a targeted biopsy of the treated lesion with one patient having been lost to follow-up following re-location. The six-month biopsy results demonstrated that, 27% of patients (10/37) achieved a clinical response, defined in this trial as no detectable tumor on targeted biopsy of the treated lesion or a sufficient reduction to deem the lesion clinically-insignificant (cancer lesion of Gleason Score 6 (pattern 3+3) and a maximum cancer core length, or MCCL, of less than 6 millimeters).

We believe the safety and biopsy data from the first administration of topsalysin supports moving forward with a single Phase 3 registration trial design using a single administration of topsalysin. We expect to obtain formal regulatory guidance on our design for a Phase 3 registration trial in the first half of 2019.

Another important objective for this Phase 2b clinical trial was to evaluate for the first time the safety of re-administering topsalysin, and to determine if additional clinical benefit could be observed, as assessed by targeted biopsy six months after a second administration of topsalysin. To be eligible to receive a second administration, patients must not have experienced any clinically-significant adverse events attributable to either topsalysin or the injection procedure. Additionally, patients must have demonstrated evidence of a response to the first treatment with topsalysin, either through a reduction in lesion size, Gleason pattern, or MCCL. No patients who had a complete ablation following the first dose received a second administration.

A review of the safety data from a total of eleven patients who received a second administration indicates that a second dose appears to be both safe and well-tolerated by patients. There were no adverse events considered related to topsalysin that were experienced by more than one patient following the second administration. The adverse events that were considered related to topsalysin were typically mild and resolved within two days. Importantly, no hypersensitivity reaction or other serious systemic reactions to topsalysin were observed. Urine function was preserved and there were no reports of sexual dysfunction related to topsalysin. As previously reported, one patient who received a second dose unfortunately experienced a serious adverse event of sudden cardiac death which, following a thorough review of medical records, serology results and autopsy findings, was considered unlikely related to topsalysin or the injection procedure by both the investigator and Company.

Based on the review of the six-month biopsy results following the second administration of topsalysin, we have concluded that there appears to be no additional clinical benefit gained with a second administration. We are reviewing the decision to include a second administration of topsalysin in any future clinical studies.

We have also completed the first of two Phase 3 clinical trials that we believe would be required to obtain marketing approval for topsalysin for the treatment of the symptoms of BPH. In October 2013, we initiated our first Phase 3 clinical trial, which we refer to as the "PLUS-1" trial, of topsalysin for the treatment of the lower urinary tract symptoms of BPH. The Phase 3 "PLUS-1" trial was an international, multicenter, randomized, double-blind, and vehicle-controlled trial to assess the efficacy and safety of a single intraprostatic administration of topsalysin (0.6 μg/g prostate) for the treatment of the lower urinary symptoms of BPH. Patients were randomized on a 1:1 ratio to either topsalysin or vehicle-only injection, and then monitored for one year. A total of 479 patients with moderate to severe BPH were enrolled and randomized by September 2014. On November 10, 2015, we announced final results from this trial. Topsalysin demonstrated a statistically significant improvement in International Prostate Symptom Score, or IPSS, total score from baseline over 12 months compared to the vehicle-only control group (7.60 vs. 6.58 point overall improvement; $p = 0.043$), the primary endpoint of the trial. IPSS is a patient recorded, composite assessment that takes into account factors such as ability to empty the bladder, frequency of urination, intermittency of urination, urgency of urination, weak strength of urine stream, straining while urinating, and having to urinate multiple times at night after going to bed. Topsalysin continues to demonstrate a favorable safety profile, with no evidence of any treatment related sexual or cardiovascular side effects.

We are not currently planning on initiating additional clinical trials, including a potential registration trial in localized prostate cancer or a second Phase 3 trial in BPH, unless we obtain additional funding or secure a development partner to fund such new clinical trials. There can be no assurance that such funding or a development partner will be available on acceptable terms or at all. Further, we cannot currently estimate when the clinical development required to seek the regulatory approvals needed to commercialize topsalysin for the treatment of clinically significant localized prostate cancer or the treatment of the symptoms of BPH will be completed.

On December 7, 2018, we entered into a Controlled Equity Offering^{SM} Sales Agreement, or the Sales Agreement, with Cantor Fitzgerald & Co., or Cantor Fitzgerald, as sales agent pursuant to which we may offer and sell from time to time, through Cantor Fitzgerald, common shares having an aggregate offering price of up to $20.0 million. We will pay Cantor Fitzgerald an amount equal to 3.0% of the aggregate gross proceeds from each sale of common shares.

Kissei Pharmaceuticals License Agreement

In April 2010, we entered into an exclusive license agreement for the development and commercialization of topsalysin (and other products covered by the licensed patent). The agreement with Kissei Pharmaceuticals Co., Ltd., a Japanese pharmaceutical company, or Kissei covers the development and commercialization of topsalysin in Japan for the treatment of the symptoms of BPH, prostate cancer, prostatitis or other diseases of the prostate. Pursuant to the agreement in 2010, we received an upfront license payment of $3.0 million. We have determined that the deliverables under this agreement included the license, the transfer of relevant technical information and participation in a periodic development meeting. we recognized the entire upfront license payment upon receipt as the license was deemed to have stand-alone value and no significant undelivered performance obligations were identified in connection with the license.

During the year ended December 31, 2013, we recorded as revenue a $5.0 million non-refundable substantive milestone payment due from Kissei upon the achievement of certain development activities during this period. In accordance with our revenue recognition policy, we recognize the receipt of milestone payments in accordance with the milestone method in the period in which the underlying triggering event occurs.

Topsalysin License Agreement for Prostate Cancer

In 2004, we licensed exclusive rights to topsalysin for the treatment of prostate cancer under an agreement with UVIC and Johns Hopkins. We have agreed to make cumulative milestone payments over the lifecycle of topsalysin of up to CND$3.6 million, or $2.6 million, as converted, on the achievement of certain clinical and regulatory milestones and to pay royalties on commercial sales of resulting products. From the inception of the agreement, we have paid milestone payments of CND$0.1 million, or $0.1 million, applying the historical conversion rate at each payment date. To date we have completed three clinical trials in patients with prostate cancer.

Topsalysin License Agreement for BPH

In 2009, we licensed exclusive rights to topsalysin under an agreement with UVIC and Johns Hopkins with respect to the use of topsalysin for the treatment of the symptoms of BPH and other non-cancer diseases and conditions of the prostate, with the exception of prostate cancer. The license agreement requires us to make payments of CND$1.3 million, or $1.0 million, as converted, on the achievement of certain clinical and regulatory milestones and to pay royalties on commercial sales of resulting products. From the inception of the agreement, we have incurred sub-license fees of $0.6 million and milestone payments of $0.1 million under this agreement.

Financial Operations Overview

Revenues

Our revenues to date consist of a $3.0 million up-front payment received from Kissei in 2010 and a $5.0 million non-refundable milestone payment for our achievement of certain development activities in 2013. We have no products approved for sale, and we have not generated any revenues from product sales.

Other than potential development milestones from Kissei, we do not expect to receive any revenues from topsalysin until we obtain regulatory approval and commercialize such product or until we potentially enter into additional collaborative agreements with third parties for the development and commercialization of topsalysin, which additional agreements will not likely occur until we complete the development of topsalysin. If our development efforts for topsalysin, or the efforts of Kissei or any future collaborator, result in clinical success and regulatory approval or collaboration agreements with other third parties, we may generate revenues from topsalysin. However, we may never generate revenues from topsalysin as we or any collaborator may never succeed in obtaining regulatory approval or commercializing this product.

Research and Development Expenses

Research and development expenses can be driven by a number of factors including: (a) the scope of clinical development and research programs pursued; (b) the type and size of clinical trials undertaken; (c) the number of clinical trials that are active during a particular period of time; (d) the rate of patient enrollment; (e) regulatory activities to support the clinical programs; and (f) Chemistry, Manufacturing and Controls, or CMC, activities associated with process development, scale-up and manufacture of drugs used in clinical trials; and such expenses are ultimately a function of decisions made to continue the development and testing of a product candidate based on supporting safety and efficacy results from clinical trial.

The majority of our operating expenses to date have been incurred in research and development activities related to topsalysin. Research and development expenses include:

- external research and development expenses incurred under agreements with clinical research organizations, or CROs, and investigative sites and clinical trial costs, as well as payments to consultants;
- third-party manufacturing expenses;
- employee related expenses, including salaries, benefits, travel and stock-based compensation expense; and
- facilities, depreciation and other allocated expenses.

We expense research and development costs as incurred. We account for nonrefundable advance payments for goods and services that will be used in future research and development activities as expenses when the service has been performed or when the goods have been consumed. Since our inception in January 2002 through December 31, 2018, we have incurred a total of $114.9 million in research and development expenses.

At this time, due to the risks inherent in the clinical trial process and given the stage of our product development program, we are unable to estimate with any certainty the costs we will incur in the continued development of topsalysin for potential approval and commercialization in two indications. Clinical development timelines, the probability of success and development costs can differ materially from expectations. However, we do expect our research and development expenses to continue for the foreseeable future as we advance topsalysin through clinical development. The process of conducting clinical trials necessary to obtain regulatory approval is costly and time consuming. Any failure by us or delay in completing clinical trials, or in obtaining regulatory approvals, could lead to increased research and development expense and, in turn, have a material adverse effect on our results of operations.

General and Administrative Expenses

General and administrative expenses consist primarily of salaries and related benefits including stock-based compensation. Other general and administrative expenses include allocated facility-related costs not otherwise included in research and development expenses, travel expenses, market research expenses and professional fees for auditing, tax, investor relations and legal services. We expect general and administrative expenses to remain fairly consistent over the next year but we do expect that general and administrative expenses will increase as we move towards commercialization of our drug candidates in future periods.

Interest Expense

Interest expense represents interest payable, amortization of our debt discount and issuance costs on our outstanding promissory notes.

Interest Income

We earn interest income from interest-bearing cash and investment accounts.

Gain (Loss) on Revaluation of Warrant Liability

In connection with the offerings completed in 2016, we issued warrants to purchase our common shares. These warrants may require us to pay the warrant holder cash under certain provisions of the warrant and therefore we account for these warrants as a liability. The fair value of these warrants is calculated utilizing a Black-Scholes pricing model. We calculated the initial fair value of these warrants at the date the warrants were issued. At each reporting date, we are required to remeasure the fair value of the warrant liability and any corresponding increase or decrease to the warrant liability is recorded as a gain (loss) on revaluation of warrant liability. In addition, if a warrant holder exercises warrants, we are required to revalue the fair value of the underlying warrants on the date of exercise and reclassify the change in the fair value from the warrant liability to contributed surplus.

Certain inputs utilized in our Black-Scholes pricing model may fluctuate in future periods based upon factors which are outside of our control. A significant change in one or more of these inputs used in the calculation of the fair value may cause a significant change to the fair value of our warrant liability which could also result in material non-cash gain or loss being reported in our consolidated statement of operations and comprehensive loss.

Loss on Early Extinguishment of Debt

On September 2, 2016, we repaid the outstanding balance of the Oxford Loan and Security Agreement in full. We made a total payoff payment of $4.2 million to Oxford, which included the final payment of $300,000, a prepayment fee of $39,000, accrued interest of $2,000 and legal fees of $4,000. We had $159,000 of unamortized debt premium as of the date of the payoff. The debt repayment was accounted for as an extinguishment as per ASC 470-50, "*Debt: Modification and Extinguishments"*, and a loss on early extinguishment of the debt totaling $180,000 was recorded for the year ended December 31, 2016, consisting of the final payment and the prepayment fee which was offset by the unamortized debt premium.

Other Expense, Net

Other expense consists primarily of foreign exchange gains and losses and on occasion income or expense of an unusual nature. Foreign exchange gains and losses result from the settlement of foreign currency transactions and from the remeasurement of monetary assets and liabilities denominated in currencies other than our functional currency.

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 consolidated financial statements, which have been prepared in conformity with generally accepted accounting principles in the United States. The preparation of our financial statements requires us to make estimates and assumptions that affect the reported amounts of assets and liabilities and the revenues and expenses incurred during the reported periods. We base our estimates on historical experience and on various other factors that we believe are reasonable under the circumstances, the results of which form the basis for making judgments about the carrying value of assets and liabilities that are not apparent from other sources. Actual results may differ from these estimates under different assumptions or conditions.

While our significant accounting policies are described in the notes to our consolidated financial statements appearing under *Item 8. Financial Statements and Supplementary Data* of this Annual Report on Form 10-K, we believe that the following accounting policies are critical to understanding and evaluating our reported financial results.

Revenue Recognition

Effective January 1, 2018, we adopted Accounting Standards Update, or ASU, No. 2014-09, "*Revenue from Contracts with Customers (Topic 606)"* and the related amendments that were issued by the Financial Accounting Standards Board, or FASB. Topic 606 establishes principles for reporting useful information to users of financial statements about the nature, amount, timing and uncertainty of revenue and cash flows arising from the entity's contracts with customers.

We may enter into product development agreements with collaborative partners for the research and development of products for the treatment of urological diseases. The terms of the agreements may include nonrefundable signing and licensing fees, development and sales-based milestone payments and royalties on any product sales derived from collaborations. To the extent that the collaborative partner is deemed to be a customer, a party that has contracted with a company to obtain goods and services that are an output of the company's ordinary activities in exchange for consideration, we will account for the product development agreement in accordance with Topic 606. We will only recognize revenue if a contract meets the following parameters: the parties have approved the contract, each party's rights to goods and services to be transferred can be identified, the payment terms are defined, the contract has commercial substance and it is probable we will collect substantially all of the consideration. Once it is determined that a contract exists, we will evaluate the performance obligations within the product development agreement. Performance obligations will be analyzed to determine whether the performance obligations are distinct or whether they must be accounted for as a single unit of multiple related distinct goods and services.

We will then perform an analysis to determine the total transaction price that we expect to receive from satisfying the performance obligations in the agreement. To the extent that the agreement includes variable consideration, amounts which can vary depending on the occurrence or nonoccurrence of a future event, the amount included in the total transaction price may be limited to the amount which is probable that a significant reversal will not occur when the uncertainty associated with the variable consideration is subsequently resolved. Development milestones associated with the successful outcome of a clinical trial or regulatory approval are highly susceptible to factors outside the influence of us and therefore any revenue associated with these milestones are not recognized as revenue until the occurrence of the event assuming its related performance obligation has been completed. Sales-based royalty revenue and sales-based milestone payments will be recognized when the later of the following events occurs: the subsequent sale occurs or the performance obligation to which some or all of the sales-based royalty or sales-based milestone payment has been allocated has been satisfied.

The calculated transaction price will then be allocated to the separate performance obligations based upon the relative standalone selling price of the performance obligations. If standalone selling price cannot be determined a residual approach may be used to estimate the standalone selling price when the selling price for a good or service is highly variable or uncertain.

For each performance obligation, we must determine the period over which the performance obligations will be satisfied, and revenue recognized. Revenue will be recognized over time if we satisfy the performance obligation over a period of time whereas revenue will be recognized at a point in time if the performance obligation is satisfied at a specific point in time

Revenue related to the transfer of an intellectual property license will be recognized either upon the transfer of the license or over a period of time depending upon whether or not the transfer of the intellectual property license is a distinct performance obligation, or the transfer of the intellectual property license is not distinct from other goods and services included in the agreement. Other factors which may impact our timing for revenue recognition related to the transfer of the license will be a determination of whether the license is a right to use our intellectual property as it exists at the point in time the license is granted or whether the license provides access to our intellectual property as it exists throughout the license period.

Accrued Research and Development Expenses

We accrue and expense activities performed by third parties based upon estimates of the percentage of work completed of the total work over the life of the agreements established with external service providers. We determine the estimates through discussions with internal clinical personnel and external service providers as to the progress or stage of completion of trials or services and the agreed-upon fee to be paid for such services based on facts and circumstances known by us as of each balance sheet date. However, actual costs and timing of clinical trials are highly uncertain, subject to risks and may change depending upon a number of factors, including our clinical development plan.

If the actual timing of the performance of services or the level of effort varies from the estimate, we will adjust the accrual accordingly. Adjustments to prior period estimates have not been material.

Examples of estimated accrued research and development expenses include:

- fees to vendors related to product development and manufacturing;
- fees to clinical research organizations in connection with clinical studies; and
- fees to investigative sites in connection with clinical studies.

Nonrefundable advance payments for goods and services that will be used or rendered in future research and development activities are recorded as a prepaid expense and recognized as expense in the period that the related goods are consumed or services are performed.

Essentially all of our research and development expenses were related to topsalysin during the years ended December 31, 2018, 2017 and 2016. We recognized research and development expenses as follows (in thousands):

	For the Years Ended December 31,		
	2018	2017	2016
Clinical research and development	$ 3,927	$ 3,908	$ 2,974
Manufacturing	6,606	1,797	421
Stock-based compensation expense	177	481	143
	$ 10,710	$ 6,186	$ 3,538

Warrant Liability

In connection with the offering we completed on May 11, 2016, we issued 1,785,714 warrants to purchase common shares. These warrants may require us to pay the warrant holder cash under certain provisions of the warrant and therefore we are accounting for these warrants as a liability. As a result of these warrants being classified as a liability, we are required to calculate the fair value of these warrants at each reporting date. The fair value of these warrants is calculated utilizing a Black-Scholes pricing model. We calculated the initial fair value of these warrants on May 11, 2016, the date the warrants were issued. 10,000 of these warrants remain outstanding from this offering with an assessed fair market value of $3,000 and $19,000 as of December 31, 2018 and 2017, respectively.

The following inputs were utilized in the Black-Scholes pricing model:

	December 31,	
	2018	2017
Stock price	$ 0.83	$ 2.27
Exercise price	$ 1.40	$ 1.40
Risk-free interest rate	2.46%	2.01%
Volatility	82.47%	143.57%
Dividend yield	0.00%	0.00%
Expected life in years	2.36	3.36
Calculated fair value per warrant	$ 0.29	$ 1.95

In connection with the offering we completed on August 26, 2016, we issued 5,606,250 warrants to purchase common shares. These warrants may require us to pay the warrant holder cash under certain provisions of the warrant and therefore we are accounting for these warrants as a liability. As a result of these warrants being classified as liabilities, we are required to calculate the fair value of these warrants at each reporting date. The fair value of these warrants are calculated utilizing a Black-Scholes pricing model. We calculated the initial fair value of these warrants on August 26, 2016, the date the warrants were issued. All of these warrants remain outstanding. The warrants outstanding from this offering have an assessed fair market value of $1.4 million and $10.1 million as of December 31, 2018 and 2017, respectively.

The following inputs were utilized in the Black-Scholes pricing model:

	December 31,	
	2018	2017
Stock price	$ 0.83	$ 2.27
Exercise price	$ 4.00	$ 4.00
Risk-free interest rate	2.45%	2.04%
Volatility	104.52%	145.36%
Dividend yield	0.00%	0.00%
Expected life in years	2.65	3.65
Calculated fair value per warrant	$ 0.25	$ 1.80

Certain inputs utilized in our Black-Scholes pricing model may fluctuate in future periods based upon factors which are outside of our control. A significant change in one or more of these inputs used in the calculation of the fair value may cause a significant change to the fair value of our warrant liability which could also result in material non-cash gain or loss being reported in our consolidated statement of operations and comprehensive loss.

A 10% change in our closing stock price on December 31, 2018 would result in a $0.2 million change to the fair value of our warrant liability at December 31, 2018. A 10% change in our stock price volatility at December 31, 2018 would result in a change of $0.3 million to our warrant liability at December 31, 2018. A 10% change in the risk-free interest rate at December 31, 2018 would not have a material effect on the fair value of our warrant liability.

Stock-Based Compensation

We expense the fair value of employee stock options using the graded vesting method over the vesting period. Stock-based compensation expense is measured using the fair value of the award at the grant date. The fair value of each stock-based award is estimated using the Black-Scholes pricing model.

Effective January 1, 2017, we adopted ASU No. 2016-09, *"Compensation – Stock Compensation (Topic 718): Improvements to Employee Share-Based Payment Accounting"*). This guidance simplified the accounting for share-based compensation. Upon adoption, we elected to no longer apply a forfeiture rate to estimate forfeitures expected to occur and instead account for forfeitures as they occur. The impact from the adoption of this new guidance to the excess tax benefits or the share-based compensation expense was not material nor was the impact on the statement of cash flows.

We recognized stock-based compensation expense as follows (in thousands):

	For the Years Ended December 31,		
	2018	2017	2016
Research and development	$ 177	$ 481	$ 143
General and administrative	683	1,231	282
Total	$ 860	$ 1,712	$ 425

As of December 31, 2018 there were $0.9 million of unrecognized compensation costs related to non-vested stock options. As of December 31, 2018 we expect to recognize those costs over a weighted average period of 1.5 years.

The fair value of options granted during the years ended December 31, 2018, 2017 and 2016 were estimated at the date of grant using the following weighted average assumptions:

	For the Years Ended December 31,		
	2018	2017	2016
Expected life of the option term (years)	4.9	4.2	3.9
Risk-free interest rate	2.5%	1.9%	1.5%
Dividend yield	0.0%	0.0%	0.0%
Volatility	127.7%	134.8%	144.0%

Expected Life of the Option Term – This is the period of time that the options granted are expected to remain unexercised. Options granted during 2018 have a contractual term of ten years. We estimate the expected life of the option term based on actual past behavior for similar options.

Risk-Free Interest Rate – This is the United States Treasury rate that most closely resembles the expected life of the option.

Dividend Yield – We have never declared or paid dividends on common shares and have no plans to do so in the foreseeable future.

Volatility – Volatility is a measure of the amount by which a financial variable such as a share price has fluctuated or is expected to fluctuate during a period. We considered the historical volatility from our Canadian initial public offering through the dates of grants.

Fair Value of Financial Instruments

We measure certain financial assets and liabilities at fair value based on the exchange price that would be received for an asset or paid for to transfer a liability (an exit price) in the principal or most advantageous market for the asset or liability in an orderly transaction between market participants. The carrying amounts of our financial instruments, including cash and cash equivalents and accounts payable and accrued expenses, approximate fair value due to their short maturities.

We follow ASC 820-10, "*Fair Value Measurements and Disclosures*," which among other things, 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 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, a three-tier fair value hierarchy has been established, which prioritizes the inputs used in measuring fair value as follows:

Level 1 – Inputs are unadjusted, quoted prices in active markets for identical assets or liabilities at the measurement date.

Level 2 – Inputs (other than quoted prices included in Level 1) are either directly or indirectly observable for the asset or liability through correlation with market data at the measurement date and for the duration of the instrument's anticipated life.

Level 3 – Inputs reflect management's best estimate of what market participants would use in pricing the asset or liability at the measurement date. Consideration is given to the risk inherent in the valuation technique and the risk inherent in the inputs to the model.

Recent Accounting Pronouncements

In February 2016, the FASB issued ASU, No. 2016-02, "*Leases (Topic 842)*", updated in July 2018 with No. 2018-11. This guidance requires lessees to recognize a lease liability and a right-of-use asset with the exception of short-term leases. In addition, lessees are required to classify leases as either operating or finance based on current criteria of whether or not the lease is effectively a financed purchase by the lessee. The new standard is effective for the annual reporting period beginning after December 15, 2018 and early adoption is permitted. Although we are in the process of evaluating the impact of this guidance on its consolidated financial statements and related disclosures, we expect that our operating lease will be subject to the new standard and recognized as an operating lease liability and right-of-use asset upon adoption.

Net Operating Loss Carryforwards

As of December 31, 2018 we had Canadian and U.S. federal tax net operating loss carryforwards of $148.4 million and $2.5 million, respectively, which begin to expire in 2026 and 2034, respectively. As of December 31, 2018, we also had Canadian investment tax credits and U.S. federal research and development tax credits of $2.4 million and $1.7 million, respectively. The Canadian investment tax credits and U.S. federal research and development tax credits will begin to expire in 2019 and 2031, respectively.

Results of Operations

Comparison of the Years Ended December 31, 2018 and 2017

The following table summarizes the results of our operations for the year ended December 31, 2018 and 2017, together with the changes in those items in dollars (in thousands):

	For the Years Ended December 31,		Change 2018 vs. 2017
	2018	2017	
Research and development expenses	$ 10,710	$ 6,186	4,524
General and administrative expenses	4,429	5,732	(1,303)
Interest expense	(684)	(207)	(477)
Interest income	333	238	95
Gain on revaluation of warrant liability	8,690	3,307	5,383
Other income (expense), net	22	(48)	70

Research and development expenses. Research and development expenses were $10.7 million in the year ended December 31, 2018 compared to $6.2 million in the year ended December 31, 2017. The increase in research and development costs is attributable to the following:

- a $4.7 million increase in costs associated with manufacturing activities for topsalysin as we move forward with our manufacturing plans to provide sufficient drug substance for a potential Phase 3 registration trial in localized prostate cancer and also a potential second Phase 3 for the treatment of the symptoms of BPH;
- a $0.2 million increase in consulting and travel costs associated with our manufacturing and regulatory activities; and
- a $0.1 million increase in legal fees associated with patent filings around our Phase 2b clinical data and our new drug product formulation.

These increases were partially offset by decreases of $0.3 million for non-cash stock-based compensation expenses and $0.2 million in personnel related costs.

General and administrative expenses. General and administrative expenses were $4.4 million in the year ended December 31, 2018 compared to $5.7 million for the year ended December 31, 2017. The decrease is primarily due to decreases in non-cash stock-based compensation expense of $0.5 million, marketing research activities of $0.4 million and personnel related costs of $0.4 million.

Interest expense. Interest expense was $0.7 million in the year ended December 31, 2018 compared to $0.2 million for the year ended December 31, 2017. The increase is related to our Silicon Valley Bank Loan and Security Agreement, which was entered into in September 2017.

Interest income. Interest income was $0.3 million for the year ended December 31, 2018 compared to $0.2 million for the year ended December 31, 2017. The increase is due to an increase in yields earned on our interest-bearing cash and investment accounts.

Gain on revaluation of warrant liability. Gain on revaluation of the warrant liability was $8.7 million for the year ended December 31, 2018 compared to $3.3 million for the year ended December 31, 2017. The non-cash gain is associated with the change in the fair value of our warrant liability which is calculated using a Black-Scholes pricing model.

Comparison of the Years Ended December 31, 2017 and 2016

The following table summarizes the results of our operations for the year ended December 31, 2017 and 2016, together with the changes in those items in dollars (in thousands):

	For the Years Ended December 31,		Change 2017 vs. 2016
	2017	2016	
Research and development expenses	$ 6,186	$ 3,538	2,648
General and administrative expenses	5,732	6,768	(1,036)
Interest expense	(207)	(373)	166
Interest income	238	37	201
Gain (loss) on revaluation of warrant liability	3,307	(330)	3,637
Loss on early extinguishment of debt	—	(180)	180
Other expense, net	(48)	(12)	36

Research and development expenses. Research and development expenses were $6.2 million in the year ended December 31, 2017 compared to $3.5 million in the year ended December 31, 2016. The increase in research and development costs is attributable to the following:

- a $2.2 million increase in costs associated with our Phase 2b clinical trial of topsalysin for the focal treatment of localized prostate cancer which was initiated in March 2017;
- a $1.3 million increase in the costs associated with manufacturing activities for topsalysin, including reformulation costs, and
- a $0.3 million increase in the non-cash stock-based compensation expense, primarily associated with stock options granted to employees in December 2016.

These increases were partially offset by decreases of $0.4 million for costs associated with our completed Phase 2a proof of concept clinical trial for low to intermediate risk prostate cancer and $0.8 million in personnel related costs, partially related to our completed reduction in work force in May 2016.

General and administrative expenses. General and administrative expenses were $5.7 million in the year ended December 31, 2017 compared to $6.8 million for the year ended December 31, 2016. The decrease of approximately $1.0 million is primarily due to the inclusion of $1.6 million in offering costs which were allocated to our liability warrants issued in both our private and public offerings which were completed in 2016. In addition, there is a decrease of $0.3 million of professional services and $0.6 million of personnel related costs from 2016 to 2017. These decreases are partially offset by increases in non-cash stock-based compensation expense of $0.9 million, market research activities of $0.4 million and consulting expense of $0.2 million. The increase in the non-cash stock-based compensation expense is primarily associated with stock options granted to employees in December 2016 and members of our Board of Directors in May 2017.

Interest expense. Interest expense was $0.2 million in the year ended December 31, 2017 compared to $0.4 million for the year ended December 31, 2016. Interest expense for the year ended December 31, 2017 is related to the Loan and Security Agreement with SVB entered into in September 2017. Interest expense for the year ended December 31, 2016 was related our Loan and Security Agreement with Oxford. We repaid the outstanding principal balance of the Oxford Loan and Security Agreement in full in September 2016.

Interest income. Interest income was $0.2 million for the year ended December 31, 2017 compared to $37,000 for the year ended December 31, 2016. The increase is partially due to the increase in the average balances of the interest-bearing cash and investment accounts period over period and also due to an increase in yields earned on our interest-bearing cash and investment accounts.

Gain (loss) on revaluation of warrant liability. Gain on revaluation of the warrant liability was $3.3 million for the year ended December 31, 2017 as compared to a loss of $0.3 million for the year ended December 31, 2016. The non-cash gain (loss) is associated with the change in the fair value of our warrant liability which is calculated using a Black-Scholes pricing model.

Loss on early extinguishment of debt. Loss on early extinguishment of debt was $0.2 million for the year ended December 31, 2016. This consists of the final payment and prepayment fee offset by our unamortized debt premium resulting from the payoff of our loan with Oxford.

Liquidity and Capital Resources

Overview

Since our inception, our operations have been primarily financed through public and private equity sales, debt financings and payments from Kissei. Since inception, we have devoted our resources to funding and conducting research and development programs, including discovery research, preclinical studies, manufacturing activities and clinical trial activities. At December 31, 2018, we had cash, cash equivalents and securities available-for-sale of $12.5 million, representing a decrease of $13.3 million from December 31, 2017. We had working capital of $8.2 million at December 31, 2018, a decrease of $15.9 million from December 31, 2017.

We expect that our cash, cash equivalents and securities available-for-sale will be sufficient to fund our operations through September 2019, as a result, substantial doubt exists over our ability to continue as a going concern from one year from the date of the issuance of our consolidated financial statements. The accompanying financial statements have been prepared on a basis which assumes we are a going concern, and does not include any adjustments to reflect the possible future effects on the recoverability and classification of assets or the amounts and classifications of liabilities that may result from any uncertainty related to our ability to continue as a going concern. If we are unable to maintain sufficient financial resources, our business, financial condition and results of operations will be materially and adversely affected. There can be no assurance that we will be able to obtain the needed financing on acceptable terms or at all. Additionally, equity or debt financings may have a dilutive effect on the holdings of our existing stockholders. These factors raise substantial doubt about our ability to continue as a going concern.

We are currently evaluating options to further advance the clinical development of topsalysin. We will require significant additional funding to advance topsalysin in clinical development. We could use dilutive funding options such as an equity financing and/or non-dilutive funding options such as a partnering arrangement to fund future clinical development of topsalysin. At this point in time we do not plan on pursuing new clinical trials, including a Phase 3 trial in localized prostate cancer or a second Phase 3 trial in BPH unless we obtain additional financing or securing a development partner. There can be no assurance that such funding or development partner will be available on acceptable terms or at all.

On March 7, 2019, we received a letter from the Listing Qualifications Staff of The Nasdaq Stock Market LLC ("Nasdaq") notifying us that for the last 30 consecutive business days prior to the date of the Notice, the market value of our listed securities was less than $35 million and therefore we did not meet the requirement for continued listing on The Nasdaq Capital Market as required by Nasdaq Listing Rule 5550(b)(2) (the "Market Value Rule") or the alternative requirements under Nasdaq Listing Rules 5550(b)(1) and 5550(b)(3). In accordance with Nasdaq Listing Rule 5810(c)(3)(C), we have 180 calendar days, or until September 3, 2019, to regain compliance with the Market Value Rule. We will regain compliance with the Market Value Rule if the market value of our listed securities closes at or above $35 million for a minimum of 10 consecutive business days anytime during the 180 day compliance period.

Shares issued in equity sales agreement

On December 7, 2018, we entered into the Sales Agreement with Cantor Fitzgerald as sales agent pursuant to which we may offer and sell from time to time, through Cantor Fitzgerald, common shares having an aggregate offering price of up to $20.0 million.

As of December 31, 2018, we issued 94,762 commons shares at a weighted average price of $1.28 for total proceeds of $121,000.

Promissory Note

On September 8, 2017, we entered into a Loan and Security Agreement with SVB. Under the terms of the agreement, we borrowed $7.0 million which bears fixed interest of 6.75% per annum. We have the option to prepay the outstanding balance of the loan in full, subject to a prepayment fee of 1% to 3% depending upon when the prepayment occurs. Upon the final repayment of the loan on the maturity date of September 1, 2021, by prepayment, or upon acceleration, we will pay SVB an additional fee of 5% of the principal amount of $7.0 million. This additional fee is recorded as a debt discount and is being recognized as interest expense over the life of the loan utilizing the effective interest method.

Under the terms of the agreement, we had the option to request an additional $3.0 million of principal. This option expired unexercised on December 31, 2018.

In September 2018, we announced that we met the requirements in our existing Loan and Security Agreement with SVB to extend the interest only periods to March 31, 2019. We will begin making interest and principal payments starting on April 1, 2019 and ending on the final payment date of September 1, 2021.

We are not subject to any financial covenants under the loan. As of December 31, 2018, we were in compliance with all covenants under the loan. The loan agreement contains customary affirmative and negative covenants, indemnification provisions and events of default. The affirmative covenants include, among others, covenants requiring us to maintain our legal existence and governmental approvals, deliver certain financial reports and maintain certain intellectual property rights. The negative covenants include, among others, restrictions on transferring or licensing our assets, changing our business, incurring additional indebtedness, engaging in mergers or acquisitions, paying dividends or making other distributions, and creating other liens on our assets, in each case subject to customary exceptions. If we default under the loan, SVB may accelerate all of our repayment obligations and take control of our pledged assets. SVB could declare a default under the loan upon the occurrence of any event that SVB interprets as a material adverse change as defined under the loan agreement, thereby requiring us to repay the loan immediately.

We issued to SVB warrants to purchase an aggregate of up to 99,526 of our common shares at an exercise price of $2.11 per share. The warrants will expire seven years from the date of the grant.

Future Operations

We have devoted substantial resources to developing topsalysin, protecting and enhancing our intellectual property and providing general and administrative support for these activities. We have not generated any revenue from product sales and, to date, have funded our operations primarily through public and private equity security sales, debt financings and payments from Kissei.

We will require significant additional capital to fund our operations and complete development of topsalysin and there is no assurance that we will obtain additional capital.

Our future capital requirements will depend on, and could increase significantly as a result of many factors, including:

- progress in, and the costs of, our clinical trials, including the costs of a Phase 3 clinical trial for localized prostate cancer trial and the cost of a second Phase 3 clinical trial for the treatment of the symptoms of BPH and other research and development activities for topsalysin;
- the costs and timing of regulatory approvals;
- our ability to maintain our strategic license with Kissei and its ability to achieve applicable milestones and establish and maintain additional strategic collaborations, including licensing and other arrangements;
- the costs involved in filing, prosecuting, enforcing and defending patent claims and other intellectual property rights;
- the costs of obtaining and securing manufacturing supply for clinical or commercial production of product candidates, including the costs associated with our current reformulation of topsalysin drug product; and
- the costs of establishing, or contracting for, sales and marketing capabilities if we obtain regulatory approvals to market topsalysin.

Until we can generate significant continuing revenues, we expect to satisfy our future cash needs through private and public sales of our securities, debt financings, by establishing additional strategic collaborations for topsalysin or from exercise of outstanding common share purchase warrants and stock options.

Cash Flows

The following table shows a summary of our cash flows for the years ended December 31, 2018, 2017 and 2016 (in thousands):

	For the Years Ended December 31,		
	2018	**2017**	**2016**
Net cash provided by (used in):			
Operating activities	$ (13,457)	$ (9,968)	$ (10,329)
Investing activities	8,267	6,323	(13,721)
Financing activities	102	6,932	30,971
Effect of exchange rate changes on cash and cash equivalents	(1)	—	(2)
Net (decrease) increase in cash and cash equivalents	$ (5,089)	$ 3,287	$ 6,919

Operating Activities

Net cash used in operating activities increased to $13.5 million for the year ended December 31, 2018 compared to $10.0 million for the year ended December 31, 2017. The increase in net cash used in operating activities of approximately $3.5 million was primarily due to an increase in research and development expenses associated with manufacturing activities for topsalysin offset in part by a decrease in funds used for the payment of accounts payable and the use of prepaid expenses and other current assets during the period.

Net cash used in operating activities decreased to $10.0 million for the year ended December 31, 2017 compared to $10.3 million for the year ended December 31, 2016. The decrease in net cash used in operating activities of approximately $0.4 million was primarily due to the net cash outflow impact of the decrease in our net loss from period to period partially offset by a decrease in funds used for the payment of accounts payable and accrued expenses for the year ended December 31, 2017.

Investing Activities

Net cash provided by investing activities was $8.3 million for the year ended December 31, 2018, compared to net cash used in investing activities of $6.3 million for the year ended December 31, 2017. The increase in net cash provided by investing activities from December 31, 2017 to December 31, 2018 represents an increase in proceeds from the maturity of our securities classified as available-for-sales to fund our operations during 2018.

Net cash provided by investing activities was $6.3 million for the year ended December 31, 2017, compared to net cash used in investing activities of $13.7 million for the year ended December 31, 2016. The increase in net cash provided by investing activities from December 31, 2016 to December 31, 2017 represents the usage of our securities classified as available-for-sale to purchase securities with maturities less than 90 days which are classified as cash and cash equivalents and the usage of the proceeds from the maturity of our securities classified as available-for-sales to fund our operations during 2017.

Financing Activities

Net cash provided by financing activities was $0.1 million for the year ended December 31, 2018, as compared to $6.9 million for the year ended December 31, 2017. The cash provided by financing activities for the year ended December 31, 2018 was related to the net cash proceeds received from the issuance of common stock in our equity sales agreement with Cantor Fitzgerald. The cash provided by financing activities for the year ended December 31, 2017 was primarily related to the receipt of $6.9 million from our Loan and Security Agreement with SVB.

Net cash provided by financing activities was $6.9 million for the year ended December 31, 2017, as compared to $31.0 million for the year ended December 31, 2016. The cash provided by financing activities for the year ended December 31, 2016 was primarily related to the receipt of the proceeds from our completed common share offerings of $33.5 million, net of issuance costs. We also received proceeds of $2.6 million from the exercise of warrants and stock options. These cash inflows were offset by $5.1 million of principal payments on our loan with Oxford.

Contractual Obligations and Commitments

Our contractual obligations represent future cash commitments and liabilities under agreements with third parties and exclude contingent liabilities for which we cannot reasonably predict future payments. Accordingly, the table below excludes contractual obligations relating to milestone and royalty payments due to third parties, all of which are contingent upon certain future events. The following is a summary of our contractual obligations as of December 31, 2018 (in thousands):

	Payments Due by Period				
	Total	Less than 1 year	1-3 years	3-5 years	More than 5 years
Operating lease obligation relating to facility[1]	$ 184	$ 130	$ 54	$ —	$ —
Principal, interest payable and additional fee under promissory notes [2]	8,089	2,531	5,558	—	—
Purchase commitments[3]	683	683	—	—	—
Total	$ 8,956	$ 3,344	$ 5,612	$ —	$ —

(1) We currently lease an office facility comprising our headquarters in San Diego, California under a non-cancelable lease. The lease, as amended, expires in May 2020 and the minimum rent is $9,517 per month, subject to annual cost of living increases, plus our pro rata share of certain operating costs and other expenses.

(2) In September 2017, we entered into a Loan and Security Agreement with Silicon Valley Bank, or SVB. The principal borrowed of $7.0 million bears fixed interest of 6.75% per annum. We have the option to prepay the outstanding balance of the loan in full, subject to a prepayment fee of 1% to 3% depending upon when the prepayment occurs. Upon the final repayment of the loan on the maturity date of September 1, 2021, by prepayment, or upon acceleration, we are required to pay SVB an additional fee of $0.3 million. This amount is reflected in the table above. The repayment terms are interest only payments through March 2019 followed by 30 monthly payments of principal and interest.

(3) This amount represents purchase commitments pursuant to our manufacturing and supply agreements with Boehringer Ingelheim RCV GmbH & Co KG, or BI, and with Vetter Pharma International, GmbH, or Vetter. We are required to schedule our manufacturing activities with BI and Vetter in advance. If we cancel any of these scheduled activities without proper notice we could be required to pay penalties from 50% to 100% of the cost of the originally scheduled activity. As such we have included the activities scheduled as of December 31, 2018 which, if cancelled, could result in us incurring penalties for cancellation.

Exclusive License Agreements

Pursuant to our topsalysin license agreement with UVIC and Johns Hopkins for the treatment of prostate cancer, we have agreed to make cumulative milestone payments over the lifecycle of topsalysin of up to CND$3.6 million, or $2.6 million, as converted, on the achievement of certain clinical and regulatory milestones and to pay royalties on commercial sales of resulting products. In addition, pursuant to our topsalysin license agreement with UVIC and Johns Hopkins for the treatment of the symptoms of BPH and other non-cancer diseases and conditions of the prostate, with the exception of prostate cancer, we are required to make payments of CND$1.3 million, or $1.0 million, as converted, on the achievement of certain clinical and regulatory milestones and to pay royalties on commercial sales of resulting products.

These payments are contingent upon achieving future clinical, regulatory and commercial milestones, and accordingly these amounts are not included in the above table.

Off-Balance Sheet Arrangements

We do not have any off-balance sheet arrangements (as defined by applicable SEC regulations) that are reasonably likely to have a current or future material effect on our financial condition, results of operations, liquidity, capital expenditures or capital resources.

Item 7A. Qualitative and Quantitative Disclosures About Market Risk

Under SEC rules and regulations, as a smaller reporting company, we are not required to provide the information required by this item.

Item 8. Financial Statements and Supplementary Data

REPORT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

To the Board of Directors and Shareholders of Sophiris Bio Inc.

Opinions on the Financial Statements and Internal Control over Financial Reporting

We have audited the accompanying consolidated balance sheets of Sophiris Bio Inc. and its subsidiaries (the "Company") as of December 31, 2018 and 2017, and the related consolidated statements of operations and comprehensive loss, of shareholders' equity, and of cash flows for each of the three years in the period ended December 31, 2018, including the related notes (collectively referred to as the "consolidated financial statements"). We also have audited the Company's internal control over financial reporting as of December 31, 2018, based on criteria established in *Internal Control - Integrated Framework* (2013) issued by the Committee of Sponsoring Organizations of the Treadway Commission (COSO).

In our opinion, the consolidated financial statements referred to above present fairly, in all material respects, the financial position of the Company as of 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 accounting principles generally accepted in the United States of America. Also in our opinion, the Company maintained, in all material respects, effective internal control over financial reporting as of December 31, 2018, based on criteria established in *Internal Control - Integrated Framework* (2013) issued by the COSO.

Substantial Doubt About the Company's Ability to Continue as a Going Concern

The accompanying consolidated financial statements have been prepared assuming that the Company will continue as a going concern. As discussed in Note 1 to the consolidated financial statements, the Company expects that its cash, cash equivalents and securities available-for-sale will be sufficient to fund its operations through September 2019, which raises substantial doubt about its ability to continue as a going concern. Management's plans in regard to these matters are also described in Note 1. The consolidated financial statements do not include any adjustments that might result from the outcome of this uncertainty.

Basis for Opinions

The Company's management is responsible for these consolidated financial statements, for maintaining effective internal control over financial reporting, and for its assessment of the effectiveness of internal control over financial reporting, included in Management's Report on Internal Control Over Financial Reporting appearing under Item 9A. Our responsibility is to express opinions on the Company's consolidated financial statements and on the Company's internal control over financial reporting 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 audits to obtain reasonable assurance about whether the consolidated financial statements are free of material misstatement, whether due to error or fraud, and whether effective internal control over financial reporting was maintained in all material respects.

Our audits of the consolidated financial statements included performing procedures to assess the risks of material misstatement of the consolidated 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 consolidated 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 consolidated financial statements. Our audit of internal control over financial reporting included obtaining an understanding of internal control over financial reporting, assessing the risk that a material weakness exists, and testing and evaluating the design and operating effectiveness of internal control based on the assessed risk. Our audits also included performing such other procedures as we considered necessary in the circumstances. We believe that our audits provide a reasonable basis for our opinions.

Definition and Limitations of Internal Control over Financial Reporting

A company's internal control over financial reporting is a process designed to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles. A company's internal control over financial reporting includes those policies and procedures that (i) pertain to the maintenance of records that, in reasonable detail, accurately and fairly reflect the transactions and dispositions of the assets of the company; (ii) provide reasonable assurance that transactions are recorded as necessary to permit preparation of financial statements in accordance with generally accepted accounting principles, and that receipts and expenditures of the company are being made only in accordance with authorizations of management and directors of the company; and (iii) provide reasonable assurance regarding prevention or timely detection of unauthorized acquisition, use, or disposition of the company's assets that could have a material effect on the financial statements.

Because of its inherent limitations, internal control over financial reporting may not prevent or detect misstatements. Also, projections of any evaluation of effectiveness to future periods are subject to the risk that controls may become inadequate because of changes in conditions, or that the degree of compliance with the policies or procedures may deteriorate.

/s/ PricewaterhouseCoopers LLP
San Diego, California
March 13, 2019

We have served as the Company's auditor since 2013.

Sophiris Bio Inc.
Consolidated Balance Sheets
(In thousands, except share amounts)

	December 31,	
	2018	**2017**
Assets:		
Current assets:		
Cash and cash equivalents	$ 10,998	$ 16,087
Securities available-for-sale	1,541	9,757
Prepaid expenses and other current assets	656	1,012
Total current assets	13,195	26,856
Property and equipment, net	4	2
Other long-term assets	—	19
Total assets	$ 13,199	$ 26,877
Liabilities and shareholders' equity:		
Current liabilities:		
Accounts payable	$ 1,862	$ 832
Accrued expenses	1,192	1,499
Current portion of promissory note	1,920	372
Total current liabilities	4,974	2,703
Long-term promissory note	5,091	6,435
Warrant liability	1,399	10,089
Total liabilities	11,464	19,227
Commitments and contingencies (Note 15)		
Shareholders' equity:		
Common shares, unlimited authorized shares, no par value; 30,205,915 and 30,111,153 shares issued and outstanding at December 31, 2018 and 2017, respectively	131,247	131,247
Contributed surplus	26,714	25,854
Accumulated other comprehensive gain	100	97
Accumulated deficit	(156,326)	(149,548)
Total shareholders' equity	1,735	7,650
Total liabilities and shareholders' equity	$ 13,199	$ 26,877

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

Sophiris Bio Inc.
Consolidated Statements of Operations and Comprehensive Loss
(In thousands, except per share amounts)

	For the Years Ended December 31,		
	2018	**2017**	**2016**
Operating expenses:			
Research and development	$ 10,710	$ 6,186	$ 3,538
General and administrative	4,429	5,732	6,768
Total operating expenses	15,139	11,918	10,306
Other income (expense):			
Interest expense	(684)	(207)	(373)
Interest income	333	238	37
Gain (loss) on revaluation of warrant liability	8,690	3,307	(330)
Loss on early extinguishment of debt	—	—	(180)
Other income (expense), net	22	(48)	(12)
Total other income (expense)	8,361	3,290	(858)
Net loss	$ (6,778)	$ (8,628)	$ (11,164)
Basic and diluted loss per share	$ (0.23)	$ (0.29)	$ (0.49)
Weighted average number of outstanding shares – basic and diluted	30,115	30,111	23,002
Other comprehensive loss:			
Unrealized gain (loss) on securities available-for-sale	3	(2)	—
Total other comprehensive loss	$ (6,775)	$ (8,630)	$ (11,164)

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

Sophiris Bio Inc.
Consolidated Statements of Shareholders' Equity
(In thousands, except share amounts)

	Common Shares		Contributed Surplus	Accumulated Deficit	Accumulated Other Comprehensive Income	Total Shareholders' Equity
	Shares	Amount				
Balance at January 1, 2016	17,244,736	$ 113,880	$ 17,683	$ (129,756)	$ 99	$ 1,906
Issuance of common shares and warrants, net of issuance cost of $1,366	11,046,428	33,534	—	—	—	33,534
Exercise of warrants	1,775,714	2,486	—	—	—	2,486
Exercise of stock options	40,766	92	—	—	—	92
Initial valuation of warrant liability upon issuance of warrants	—	(18,747)	—	—	—	(18,747)
Valuation of exercised warrants reclassified from warrant liability to contributed surplus	—	—	5,681	—	—	5,681
Change in the fair value of stock-based compensation liability recorded to contributed surplus	—	—	111	—	—	111
Stock-based compensation expense	—	—	425	—	—	425
Net loss	—	—	—	(11,164)	—	(11,164)
Balance at December 31, 2016	30,107,644	$ 131,245	$ 23,900	$ (140,920)	$ 99	$ 14,324
Exercise of stock options	3,509	2	—	—	—	2
Issuance of warrants with secured promissory note	—	—	185	—	—	185
Change in the fair value of stock-based compensation liability recorded to contributed surplus	—	—	57	—	—	57
Stock-based compensation expense	—	—	1,712	—	—	1,712
Net loss	—	—	—	(8,628)	—	(8,628)
Other comprehensive loss	—	—	—	—	(2)	(2)
Balance at December 31, 2017	30,111,153	$ 131,247	$ 25,854	$ (149,548)	$ 97	$ 7,650
Issuance of common shares, net of issuance cost of $121	94,762	—	—	—	—	—
Stock-based compensation expense	—	—	860	—	—	860
Net loss	—	—	—	(6,778)	—	(6,778)
Other comprehensive gain	—	—	—	—	3	3
Balance at December 31, 2018	30,205,915	$ 131,247	$ 26,714	$ (156,326)	$ 100	$ 1,735

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

Sophiris Bio Inc.
Consolidated Statements of Cash Flows
(In thousands)

	For the Years Ended December 31,		
	2018	**2017**	**2016**
Cash flows used in operating activities			
Net loss for the period	$ (6,778)	$ (8,628)	$ (11,164)
Adjustments to reconcile net loss to net cash used in operating activities:			
Stock-based compensation	860	1,712	425
Amortization of debt discount	149	44	81
Amortization of promissory note issuance costs	56	17	—
Depreciation of property and equipment	2	4	12
Amortization of premium/discount on securities available-for-sale	(51)	116	20
Change in fair value warrant liability	(8,690)	(3,307)	330
Noncash portion of loss on early extinguishment of debt	—	—	(159)
Payment of original issue discount	—	—	(124)
Foreign exchange transaction loss	8	6	—
Changes in operating assets and liabilities:			
Prepaid expenses and other current assets	373	(37)	(499)
Accounts payable	963	374	(446)
Accrued expenses	(349)	(269)	1,195
Net cash used in operating activities	(13,457)	(9,968)	(10,329)
Cash flows provided by (used in) investing activities			
Purchases of property and equipment	(4)	(3)	—
Maturity of securities available-for-sale	11,887	22,161	2,750
Purchases of securities available-for-sale	(3,616)	(15,835)	(16,471)
Net cash provided by (used in) investing activities	8,267	6,323	(13,721)
Cash flows provided by financing activities			
Proceeds from the issuance of common shares and warrants, net of paid issuance costs	102	—	33,534
Proceeds from the exercise of warrants	—	—	2,486
Proceeds from exercise of stock options	—	2	92
Proceeds from the issuance of the Silicon Valley Bank promissory note, net of issuance costs	—	6,930	—
Principal payments on the Oxford promissory notes	—	—	(5,141)
Net cash provided by financing activities	102	6,932	30,971
Effect of exchange rate changes on cash and cash equivalents	(1)	—	(2)
Net (decrease) increase in cash and cash equivalents	(5,089)	3,287	6,919
Cash and cash equivalents at beginning of period	16,087	12,800	5,881
Cash and cash equivalents at end of period	$ 10,998	$ 16,087	$ 12,800
Supplemental disclosures of cash flow information			
Cash paid for interest	$ 479	$ 105	$ 334

	For the Years Ended December 31,		
	2018	2017	2016
Supplemental disclosures of non-cash investing and financing activities			
Valuation of warrant liability upon issuance of warrants	$ —	$ —	$ 18,747
Value of warrants issued in connection with the Silicon Valley Bank promissory note	$ —	$ 185	$ —
Valuation of exercised warrants reclassified from warrant liability to contributed surplus	$ —	$ —	$ 5,681
Change in the fair value of stock-based compensation liability recorded to contributed surplus	$ —	$ (57)	$ (111)
Unrealized loss on securities available-for sale	$ 3	$ 2	$ —
Issuance costs included in accounts payable and accrued expenses but not paid	$ 102	$ —	$ —

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

Sophiris Bio Inc.

Notes to the Consolidated Financial Statements

1. Nature of the business

Company

Sophiris Bio Inc., or the Company, or Sophiris, is a clinical-stage biopharmaceutical company focused on innovative products for the treatment of urological diseases. The Company is governed by the British Columbia Business Corporations Act. The Company's operations were initially located in Vancouver, British Columbia until April 2011, when its core activities and headquarters relocated from Vancouver, British Columbia to San Diego, California.

The consolidated financial statements include the accounts of Sophiris and its wholly-owned subsidiaries, Sophiris Bio Corp. and Sophiris Bio Holding Corp., both of which are incorporated in the State of Delaware.

Liquidity

The consolidated financial statements have been prepared on a going concern basis, which contemplates the realization of assets and the settlement of liabilities in the normal course of business. At December 31, 2018, the Company had cash, cash equivalents and securities available-for-sale of $12.5 million. The Company expects that its cash, cash equivalents and securities available-for-sale will be sufficient to fund its operations through September 2019 and, as a result, substantial doubt exists over the Company's ability to continue as a going concern from one year from the date of the issuance of its consolidated financial statements.

The Company is currently evaluating options to further advance the clinical development of topsalysin. The Company will require significant additional funding to advance topsalysin in clinical development. The Company could use dilutive funding options such as an equity financing and/or non-dilutive funding options such as a partnering arrangement to fund future clinical development of topsalysin. At this point in time the Company does not plan on pursuing new clinical trials, including a Phase 3 in localized prostate cancer or a second Phase 3 trial in benign prostatic hyperplasia, or BPH, unless the Company obtains additional financing or securing a development partner. There can be no assurance that such funding or development partner will be available on acceptable terms or at all.

If the Company is unable to raise additional capital to fund its development program efforts in sufficient amounts or on terms acceptable to it, the Company may have to significantly delay, scale back or discontinue the development and commercialization of topsalysin.

On March 7, 2019, the Company received a letter from the Listing Qualifications Staff of The Nasdaq Stock Market LLC ("Nasdaq") notifying the Company that for the last 30 consecutive business days prior to the date of the Notice, the market value of the Company's listed securities was less than $35 million and therefore the Company did not meet the requirement for continued listing on The Nasdaq Capital Market as required by Nasdaq Listing Rule 5550(b)(2) (the "Market Value Rule") or the alternative requirements under Nasdaq Listing Rules 5550(b)(1) and 5550(b)(3). In accordance with Nasdaq Listing Rule 5810(c)(3)(C), the Company has 180 calendar days, or until September 3, 2019, to regain compliance with the Market Value Rule. The Company will regain compliance with the Market Value Rule if the market value of the Company's listed securities closes at or above $35 million for a minimum of 10 consecutive business days anytime during the 180 day compliance period.

2. Summary of significant accounting policies

Significant accounting policies followed by the Company in the preparation of its consolidated financial statements are as follows:

Basis of consolidation

The consolidated financial statements include the accounts of the Company, Sophiris Bio Corp. and Sophiris Bio Holding Corp. All intercompany balances and transactions have been eliminated for purposes of consolidation.

Basis of presentation and use of estimates

The accompanying consolidated financial statements have been prepared in conformity with generally accepted accounting principles in the United States or GAAP.

GAAP requires the Company's management to make estimates and judgments that may affect the reported amounts of assets, liabilities, revenue, expenses and related disclosures. The Company bases estimates and judgments on historical experience and on various other factors that it believes to be reasonable under the circumstances. The significant estimates in these consolidated financial statements include stock-based compensation expense, fair value of the warrant liability and accrued research and development expenses. The Company's actual results may differ from these estimates. The Company evaluates its estimates on an ongoing basis. Changes in estimates are reflected in reported results in the period in which they become known by the Company's management.

Foreign currency

Historically gains and losses resulting from foreign currency translation were recorded in accumulated other comprehensive gain (loss), which is a separate component of shareholders' equity. Foreign currency transaction gains and losses are recognized as a component of other expense.

Cash and cash equivalents

Cash equivalents are short-term, highly liquid investments with an original maturity of three months or less at the date of purchase.

Securities available-for-sale

Investments with an original maturity of more than three months when purchased have been classified by management as securities available-for-sale. Such investments are carried at fair value, with unrealized gains and losses included as a component of accumulated other comprehensive gain (loss) in shareholders' equity. Realized gains and losses and declines in value judged to be other-than-temporary on available-for-sale securities are included in interest income. No other-than-temporary impairments were identified for the investment securities held by the Company as of December 31, 2018 and 2017. The cost of investment securities classified as available-for-sale is adjusted for amortization of premiums and accretion of discounts to maturity. Such amortization and accretion are included in interest income. The cost of securities sold is based on the specific-identification method. The Company has classified all of its investment securities as available-for-sale, including any of those with maturities beyond one year, as current assets on the consolidated balance sheets based on the highly liquid nature of the investment securities and because these investment securities are considered available for use in current operations.

Concentration of credit risk

Financial instruments, which potentially subject the Company to concentration of credit risk, consist primarily of cash and cash equivalents and investment securities classified as available-for-sale. The Company maintains deposits in federally insured financial institutions in excess of federally insured limits. Management believes that the Company is not exposed to significant credit risk due to the financial position of the depository institutions in which those deposits are held. Additionally, the Company has adopted an investment policy that includes guidelines relative to credit quality, diversification of maturities and liquidity.

Property and equipment

Property and equipment are recorded at cost and depreciated using the straight-line method, based on their estimated useful lives as follows:

Asset classification	Estimated useful life (in years)
Equipment	3 - 5
Computer hardware	3
Software	3 - 5
Leasehold improvements	Lesser of useful life or lease term
Furniture and fixtures	5

Repairs and maintenance costs are expensed as incurred.

The Company reviews its long-lived assets for impairment whenever events or changes in business circumstances indicate that the carrying amount of assets may not be fully recoverable or that the useful lives of these assets are no longer appropriate. Each impairment test is based on a comparison of the undiscounted cash flow to the recorded value of the asset. If impairment is indicated, the asset will be written down to its estimated fair value on a discounted cash flow basis. The Company has not recognized any impairment losses for the years ended December 31, 2018, 2017 and 2016.

Promissory notes

Promissory notes are recognized initially at fair value. Promissory notes are subsequently carried at amortized cost; any difference between the initial fair market value and the redemption value is recognized in the statement of operations and comprehensive loss over the period of the notes payable using the effective interest method.

The fair value of the promissory notes when issued with equity classified instruments is recognized initially at its relative fair value, with the fair value of the promissory note estimated using the net present value of similar promissory notes issued on a standalone basis. The equity classified instruments that are issued with the borrowings are valued at fair value using the Black-Scholes valuation model.

Revenue recognition

Effective January 1, 2018, the Company adopted Accounting Standards Update, or ASU, No. 2014-09, "*Revenue from Contracts with Customers (Topic 606)*", and the related amendments that were issued by the Financial Accounting Standards Board, or FASB. Topic 606 establishes principles for reporting useful information to users of financial statements about the nature, amount, timing and uncertainty of revenue and cash flows arising from the entity's contracts with customers.

The Company may enter into product development agreements with collaborative partners for the research and development of products for the treatment of urological diseases. The terms of the agreements may include nonrefundable signing and licensing fees, development and sales-based milestone payments and royalties on any product sales derived from collaborations. To the extent that the collaborative partner is deemed to be a customer, a party that has contracted with a company to obtain goods and services that are an output of the company's ordinary activities in exchange for consideration, the Company will account for the product development agreement in accordance with Topic 606. The Company will only recognize revenue if a contract meets the following parameters: the parties have approved the contract, each party's rights to goods and services to be transferred can be identified, the payment terms are defined, the contract has commercial substance and it is probable the Company will collect substantially all of the consideration. Once it is determined that a contract exists, the Company will evaluate the performance obligations within the product development agreement. Performance obligations will be analyzed to determine whether the performance obligations are distinct or whether they must be accounted for as a single unit of multiple related distinct goods and services.

The Company will then perform an analysis to determine the total transaction price that the Company expects to receive from satisfying the performance obligations in the agreement. To the extent that the agreement includes variable consideration, amounts which can vary depending on the occurrence or nonoccurrence of a future event, the amount included in the total transaction price may be limited to the amount which is probable that a significant reversal will not occur when the uncertainty associated with the variable consideration is subsequently resolved. Development milestones associated with the successful outcome of a clinical trial or regulatory approval are highly susceptible to factors outside the influence of the Company and therefore any revenue associated with these milestones are not recognized as revenue until the occurrence of the event assuming its related performance obligation has been completed. Sales-based royalty revenue and sales-based milestone payments will be recognized when the later of the following events occurs: the subsequent sale occurs or the performance obligation to which some or all of the sales-based royalty or sales-based milestone payment has been allocated has been satisfied.

The calculated transaction price will then be allocated to the separate performance obligations based upon the relative standalone selling price of the performance obligations. If standalone selling price cannot be determined, a residual approach may be used to estimate the standalone selling price when the selling price for a good or service is highly variable or uncertain.

For each performance obligation, the Company must determine the period over which the performance obligations will be satisfied, and revenue recognized. Revenue will be recognized over time if the Company satisfies the performance obligation over a period of time whereas revenue will be recognized at a point in time if the performance obligation is satisfied at a specific point in time.

Revenue related to the transfer of an intellectual property license will be recognized either upon the transfer of the license or over a period of time depending upon whether or not the transfer of the intellectual property license is a distinct performance obligation, or the transfer of the intellectual property license is not distinct from other goods and services included in the agreement. Other factors which may impact the Company's timing for revenue recognition related to the transfer of the license will be a determination of whether the license is a right to use the Company's intellectual property as it exists at the point in time the license is granted or whether the license provides access to the Company's intellectual property as it exists throughout the license period.

Research and development expenses

Research and development costs are charged to expense as incurred. Research and development expenses comprise costs incurred in performing research and development activities, including personnel-related costs, stock-based compensation, facilities, research-related overhead, clinical trial costs, contracted services, manufacturing, license fees and other external costs. The Company accounts for nonrefundable advance payments for goods and services that will be used in future research and development activities as expenses when the service has been performed or when the goods have been consumed rather than when the payment is made.

Accrued research and development expenses

The Company accrues and expenses activities performed by third parties based upon estimates of the percentage of work completed of the total work over the life of the agreements established with external service providers. The Company determines the estimates through discussions with internal clinical personnel and external service providers as to the progress or stage of completion of trials or services and the agreed-upon fee to be paid for such services based on facts and circumstances known to the Company as of each balance sheet date. However, actual costs and timing of clinical trials are highly uncertain, subject to risks and may change depending upon a number of factors, including the Company's clinical development plan.

If the actual timing of the performance of services or the level of effort varies from the estimate, the Company will adjust the accrual accordingly. Adjustments to prior period estimates have not been material.

Examples of estimated accrued research and development expenses include:

- fees to vendors related to product manufacturing, development and distribution of clinical supplies.
- fees to clinical research organizations in connection with clinical studies; and
- fees to investigative sites in connection with clinical studies.

Nonrefundable advance payments for goods and services that will be used or rendered in future research and development activities, are recorded as a prepaid expense and recognized as expense in the period that the related goods are consumed or services are performed.

Dividend policy

The Company has never declared or paid any cash dividends on its capital shares. The Company intends to retain all available funds and any future earnings to support its operations and finance the growth and development of its business. The Company does not intend to pay cash dividends on its common shares for the foreseeable future. Any future determination related to the Company's dividend policy will be made at the discretion of its board of directors and will depend upon, among other factors, our results of operations, financial condition, capital requirements, contractual restrictions, business prospects and other factors of the Company's board of directors may deem relevant. In addition, the Company's Loan and Security Agreement with Silicon Valley Bank, or SVB, contains a negative covenant which prohibits the Company from paying dividends without the prior written consent of SVB.

Stock-based compensation

The Company expenses the fair value of employee stock options over the vesting period. Compensation expense is measured using the fair value of the award at the grant date. The fair value of each stock-based award is estimated using the Black-Scholes pricing model and is expensed using the graded vesting method over the vesting period.

Effective January 1, 2017, the Company adopted ASU No. 2016-09, "*Compensation – Stock Compensation (Topic 718): Improvements to Employee Share-Based Payment Accounting*". This guidance simplified the accounting for share-based compensation. Upon adoption, the Company elected to no longer apply a forfeiture rate to estimate forfeitures expected to occur and instead account for forfeitures as they occur. The impact from the adoption of this new guidance to the excess tax benefits or the share-based compensation expense was not material nor was the impact on the statement of cash flows.

Prior to the Company's initial public offering, or IPO, the Company had issued its stock options with a Canadian dollar denominated exercise price. Subsequent to the Company's IPO, the Company issues its stock options with a U.S. dollar denominated exercise price.

Effective November 13, 2013, the Company voluntarily delisted from the Toronto Stock Exchange, or TSX. As a result of the delisting from the TSX and the change in the Company's functional currency to the U.S. dollar, the stock options granted with exercise prices denominated in Canadian dollars were considered dual indexed as defined in Accounting Standards Codification, or ASC, topic 718, "*Compensation, Stock Compensation*". As a result, the Company was required to account for these stock options as a liability. The fair value of the stock-based compensation liability was zero at December 31, 2017. The change in the fair value of the stock-based compensation liability was recorded as an adjustment to Contributed Surplus of ($57,000) for the year ended December 31, 2017. All of the stock options with exercise prices denominated in Canadian dollars expired on January 9, 2018. Subsequent to this date, all of the Company's stock options had exercise prices denominated in US dollars.

Warrant liability

In connection with the offerings the Company completed in the year ended December 31, 2016, the Company issued warrants to purchase common shares. These warrants may require the Company to pay the warrant holder cash under certain provisions of the warrant and therefore the Company is accounting for these warrants as a liability in accordance with ASC 480 "*Distinguishing Liabilities from Equity*". As a result of these warrants being classified as liabilities, the Company is required to calculate the fair value of these warrants at each reporting date. The fair value of these warrants are calculated utilizing a Black-Scholes pricing model. The Company calculated the initial fair value of these warrants at the date the warrants were issued. At each reporting date the Company is required to remeasure the fair value of the warrant liability and any corresponding increase or decrease to the warrant liability is recorded as a component of other income or expense in our consolidated statement of operations and comprehensive loss. In addition, if a warrant holder exercises warrants the Company is required to revalue the fair value of the underlying warrants on the date of exercise and reclassify the change in the fair value from the warrant liability to contributed surplus.

Certain inputs utilized in the Company's Black-Scholes pricing model may fluctuate in future periods based upon factors which are outside of the Company's control. A significant change in one or more of these inputs used in the calculation of the fair value may cause a significant change to the fair value of our warrant liability which could also result in material non-cash gain or loss being reported in our consolidated statement of operations and comprehensive loss.

Income taxes

The Company accounts for income taxes under the asset and liability method. Under this method, deferred tax assets and liabilities are recognized for the estimated future tax consequences attributable to differences between financial statement carrying amounts of existing assets and liabilities and their respective tax bases. Deferred tax assets and liabilities are measured using enacted rates in effect for the year in which these temporary differences are expected to be recovered or settled. Valuation allowances are provided if, based on the weight of available evidence, it is more likely than not that some or all of the deferred tax assets will not be realized.

The Company provides reserves for potential payments of tax to various tax authorities related to uncertain tax positions and other issues. Reserves are based on a determination of whether and how much of a tax benefit taken by the Company in its tax filing is more likely than not to be realized following resolution of any potential contingencies present related to the tax benefit. Potential interest and penalties associated with such uncertain tax positions are recorded as components of income tax expense.

Segment reporting

Operating segments are identified as components of an enterprise about which separate discrete financial information is available for evaluation by the chief operating decision-maker, or CODM. The Company's Chief Executive Officer serves as its CODM. The Company views its operations and manages its business as one segment operating primarily in the United States.

Fair value of financial instruments

The Company measures certain financial assets and liabilities at fair value based on the exchange price that would be received for an asset or paid for to transfer a liability (an exit price) in the principal or most advantageous market for the asset or liability in an orderly transaction between market participants. The carrying amounts of the Company's financial instruments, including cash equivalents, accounts payable and accrued expenses, approximate fair value due to their short maturities.

The Company follows ASC 820-10, "*Fair Value Measurements and Disclosures*, " which among other things, 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 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, a three-tier fair value hierarchy has been established, which prioritizes the inputs used in measuring fair value as follows:

Level 1 – Inputs are unadjusted, quoted prices in active markets for identical assets or liabilities at the measurement date.

Level 2 – Inputs (other than quoted prices included in Level 1) are either directly or indirectly observable for the asset or liability through correlation with market data at the measurement date and for the duration of the instrument's anticipated life.

Level 3 – Inputs reflect management's best estimate of what market participants would use in pricing the asset or liability at the measurement date. Consideration is given to the risk inherent in the valuation technique and the risk inherent in the inputs to the model.

Recent accounting pronouncements

In February 2016, the FASB issued ASU No. 2016-02, "*Lease*s *(Topic* 842*)* ", updated in July 2018 with No. 2018-11. This guidance requires lessees to recognize a lease liability and a right-of-use asset with the exception of short-term leases. In addition, lessees are required to classify leases as either operating or finance based on current criteria of whether or not the lease is effectively a financed purchase by the lessee. The new standard is effective for the annual reporting period beginning after December 15, 2018 and early adoption is permitted. Although the Company is in the process of evaluating the impact of this guidance on its consolidated financial statements and related disclosures, the Company expects that its operating lease will be subject to the new standard and recognized as operating lease liabilities and right-of-use assets upon adoption.

In August 2016, the FASB issued ASU 2016-15, "*Statement of Cash Flows (Topic 230): Classification of Certain Cash Receipts and Cash Payments*", addressing eight specific cash flow issues in an effort to reduce diversity in practice. The Company adopted this standard in the first quarter of 2018, and the adoption did not have an impact on the Company's consolidated financial statements.

In May 2017, the FASB issued ASU No. 2017-09, "*Compensation - Stock Compensation (Topic 718): Scope of Modification Accounting*". The new standard provides guidance about which changes to the terms or conditions of a share-based payment award require an entity to apply modification accounting in Topic 718. The new standard became effective for the Company on January 1, 2018. The adoption of this standard did not have a material impact on the Company's financial position or results of operations.

3. Net loss per common share

Basic net loss per share is calculated by dividing the net loss attributable to common shareholders by the weighted-average number of common shares outstanding during the period, without consideration for potentially dilutive securities. Diluted net loss per share is computed by dividing the net loss by the weighted-average number of potentially dilutive securities outstanding for the period determined using the treasury-stock method. For purposes of this calculation, stock options and warrants are considered to be potentially dilutive securities and are only included in the calculation of diluted net loss per share when their effect is dilutive.

The following table presents the computation of basic and diluted net loss per share (in thousands, except per share amounts):

	For the Years Ended December 31,		
	2018	2017	2016
Net loss per share:			
Net loss	$ (6,778)	$ (8,628)	$ (11,164)
Weighted-average common shares – basic and diluted	30,115	30,111	23,002
Net loss per share – basic and diluted per share	$ (0.23)	$ (0.29)	$ (0.49)

The following dilutive securities have been excluded from the computation of diluted weighted-average shares outstanding as of the year ended December 31, 2018, 2017 and 2016 as the Company recorded a net loss in all periods and, therefore, they would be anti-dilutive (in thousands):

	For the Years Ended December 31,		
	2018	2017	2016
Options to purchase common shares	2,950	2,931	2,868
Common share purchase warrants	5,798	5,825	5,965

4. Securities available-for-sale

Securities available-for-sale consisted of the following as of December 31, 2018 (in thousands):

	December 31, 2018			
	Amortized Cost	Unrealized Gain	Unrealized Loss	Estimated Fair Value
Commercial paper	$ 892	$ —	$ —	$ 892
U.S. government sponsored enterprise securities	649	—	—	649
	$ 1,541	$ —	$ —	$ 1,541

As of December 31, 2018, all of the Company's securities available-for-sale have a maturity date of less than one year.

Securities available-for-sale consisted of the following as of December 31, 2017 (in thousands):

	December 31, 2017			
	Amortized Cost	Unrealized Gain	Unrealized Loss	Estimated Fair Value
Commercial paper	$ 3,590	$ —	$ —	$ 3,590
U.S. government sponsored enterprise securities	4,985	—	(2)	4,983
Corporate debt securities	1,184	—	—	1,184
	$ 9,759	$ —	$ (2)	$ 9,757

As of December 31, 2017, all of the Company's securities available-for-sale have a maturity date of less than one year.

5. Fair value measurement and financial instruments

As of December 31, 2018, the Company has $11.9 million of securities consisting of money market funds, commercial paper and U.S. government sponsored enterprise securities with maturities that range from two days to six months with an overall average time to maturity of approximately one month. The Company has the ability to liquidate these investments without restriction. The Company determines fair value for securities with Level 1 inputs through quoted market prices. The Company determines fair value for securities with Level 2 inputs through broker or dealer quotations or alternative pricing sources with reasonable levels of price transparency. The Company's Level 2 securities have been initially valued at the transaction price and subsequently valued, at the end of each reporting period, typically utilizing third party pricing services or other observable market data. The pricing services utilize industry standard valuation models, including both income and market based approaches and observable market inputs to determine value. These observable market inputs include reportable trades, benchmark yields, credit spreads, broker/dealer quotes, bids, offers, and other industry and economic events. The Company's Level 3 inputs are unobservable inputs based on the Company's assessment that market participants would use in pricing the instruments.

The following table presents the Company's assets and liabilities that are measured at fair value on a recurring basis for the periods presented (in thousands):

	December 31, 2018	Level 1	Level 2	Level 3
Assets:				
Money market funds	$ 20	$ 20	$ —	$ —
Commercial paper	9,729	—	9,729	—
U.S. government sponsored enterprise securities	2,198	—	2,198	—
Total assets	$ 11,947	$ 20	$ 11,927	$ —
Liabilities:				
Warrant liability	$ 1,399	$ —	$ —	$ 1,399
Total liabilities	$ 1,399	$ —	$ —	$ 1,399

	December 31, 2017	Level 1	Level 2	Level 3
Assets:				
Money market funds	$ 34	$ 34	$ —	$ —
Commercial paper	19,020	—	19,020	—
U.S. government sponsored enterprise securities	4,983	—	4,983	—
Corporate debt securities	1,184	—	1,184	—
Total assets	$ 25,221	$ 34	$ 25,187	$ —
Liabilities:				
Warrant liability	$ 10,089	$ —	$ —	$ 10,089
Total liabilities	$ 10,089	$ —	$ —	$ 10,089

Warrant liability

In connection with the offering completed on May 11, 2016, the Company issued 1,785,714 warrants to purchase its common shares. These warrants may require the Company to pay the warrant holder cash under certain provisions of the warrant and therefore the Company is accounting for these warrants as a liability. As a result of these warrants being classified as a liability, the Company is required to calculate their fair value at each reporting date. The fair value of these warrants is calculated utilizing a Black-Scholes pricing model. The Company calculated the initial fair value of these warrants on May 11, 2016, the date the warrants were issued. As of December 31, 2018, only 10,000 of these warrants remain outstanding for which the fair value was remeasured as of December 31, 2018. The following inputs were utilized in the Black-Scholes pricing model:

	December 31, 2018	December 31, 2017
Stock price at the end of each reporting period	$ 0.83	$ 2.27
Exercise price	$ 1.40	$ 1.40
Risk-free interest rate	2.46%	2.01%
Volatility	82.47%	143.57%
Dividend yield	0.00%	0.00%
Expected life in years	2.36	3.36
Calculated fair value per warrant	$ 0.29	$ 1.95

In connection with the offering completed on August 26, 2016, the Company issued 5,606,250 warrants to purchase its common shares. These warrants may require the Company to pay the warrant holder cash under certain provisions of the warrant and therefore the Company is accounting for these warrants as a liability. As a result of these warrants being classified as a liability, the Company is required to calculate the fair value of these warrants at each reporting date. The fair value of these warrants is calculated utilizing a Black-Scholes pricing model. The Company calculated the initial fair value of these warrants on August 26, 2016, the date the warrants were issued. As of December 31, 2018, all of these warrants remain outstanding for which the fair value was remeasured. The following inputs were utilized in the Black-Scholes pricing model:

	December 31,	
	2018	2017
Stock price at the end of each reporting period	$ 0.83	$ 2.27
Exercise price	$ 4.00	$ 4.00
Risk-free interest rate	2.45%	2.04%
Volatility	104.52%	145.36%
Dividend yield	0.00%	0.00%
Expected life in years	2.65	3.65
Calculated fair value per warrant	$ 0.25	$ 1.80

The following table presents a reconciliation of the warrant liability measured at fair value using unobservable inputs (Level 3) (in thousands):

	For the Years Ended December 31,	
	2018	2017
Balance at beginning of period	$ 10,089	$ 13,396
Change in the fair value of warrant liability	(8,690)	(3,307)
Balance at end of period	$ 1,399	$ 10,089

The Company recognizes transfers into and out of levels within the fair value hierarchy at the end of the reporting period in which the actual event or change in circumstances that caused the transfer occurs. There were no transfers of assets or liabilities between the fair value measurement classifications.

6. Prepaid expenses and other current assets

Prepaid expenses as of December 31, 2018 and 2017 consisted of the following (in thousands):

	December 31,	
	2018	2017
Prepaid insurance	$ 245	$ 233
Prepaid research and development expenses	256	709
Other prepaid expenses and other current assets	155	70
Prepaid expenses and other current assets	$ 656	$ 1,012

As of December 31, 2018 and 2017, prepaid research and development expenses includes $0.2 million and $0.7 million, respectively for upfront fees paid to the Company's clinical research organization assisting with the Company's clinical trials and to a third-party manufacturers for the development of topsalysin. The upfront fees will be relieved in future periods based upon work completed.

7. Property and equipment

Property and equipment consisted of the following (in thousands):

	December 31,	
	2018	2017
Equipment	$ 6	$ 5
Computer hardware and software	17	20
Leasehold improvements	156	156
Furniture and fixtures	70	72
	249	253
Less: accumulated depreciation	(245)	(251)
Property and equipment, net	$ 4	$ 2

Depreciation expense was $2,000, $4,000 and $12,000 for the years ended December 31, 2018, 2017 and 2016, respectively.

8. Accrued expenses

Accrued expenses as of December 31, 2018 and 2017 consisted of the following (in thousands):

	December 31,	
	2018	2017
Accrued personnel related costs	$ 209	$ 904
Accrued interest	41	41
Accrued research and development expenses	586	273
Accrued audit and tax services	168	246
Other accrued expenses	188	35
Accrued expenses	$ 1,192	$ 1,499

9. Promissory notes

On September 2, 2016, the Company repaid the outstanding principal balance on its Loan and Security Agreement with Oxford Finance LLC, or Oxford.

On September 8, 2017, the Company entered into a new Loan and Security Agreement with Silicon Valley Bank, or SVB. Under the terms of the agreement, the Company borrowed $7.0 million which bears fixed interest of 6.75% per annum. The Company has the option to prepay the outstanding balance of the loan in full, subject to a prepayment fee of 1% to 3% depending upon when the prepayment occurs. Upon the final repayment of the loan on the maturity date of September 1, 2021, by prepayment, or upon acceleration, the Company will pay SVB an additional fee of 5% of the principal amount of $7.0 million. This additional fee was recorded as a debt discount and is being recognized as interest expense over the life of the loan utilizing the effective interest method.

Under the terms of the agreement, the Company had the option to request an additional $3.0 million of principal. The Company decided to not exercise the option to drawdown the additional $3.0 million of principal and this option expired at December 31, 2018.

In September 2018, the Company announced that it had met the requirements within its existing Loan and Security Agreement with SVB to extend the interest only periods to March 31, 2019. The Company will begin making interest and principal payments starting on April 1, 2019 and ending on the final payment date of September 1, 2021.

Pursuant to the first tranche of the loan, the Company issued warrants to SVB to purchase an aggregate of up to 99,526 of the Company's common shares at an exercise price of $2.11 per share. The warrants will expire seven years from the date of the grant. The fair value of $0.2 million for this equity component was derived using the Black-Scholes pricing model utilizing the following inputs: risk-free interest rate – 1.9%, volatility – 113.9%, dividend yield – 0% and expected life in years – 7. The $7.0 million proceeds were allocated to equity and the debt based on their relative fair values. The equity component was recognized as a debt discount and will be amortized to interest expense over the life of the debt. Interest on the loan, consisting of the stated interest rate, final payment fee and amortization of the discount, is being recognized under the effective interest method.

The third party issuance costs incurred related to the loan of $0.1 million are being amortized under the effective interest method over the life of the loan and have been recorded as a reduction to the loan balance.

In connection with the loan, the Company granted to SVB a security interest in all of the Company's personal property now owned or hereafter acquired, excluding intellectual property and certain other assets.

The Company is not subject to any financial covenants under the loan. As of December 31, 2018, the Company was in compliance with all covenants under the loan. The loan agreement contains customary affirmative and negative covenants, indemnification provisions and events of default. The affirmative covenants include, among others, covenants requiring us to maintain our legal existence and governmental approvals, deliver certain financial reports and maintain certain intellectual property rights. The negative covenants include, among others, restrictions on transferring or licensing our assets, changing our business, incurring additional indebtedness, engaging in mergers or acquisitions, paying dividends or making other distributions, and creating other liens on our assets, in each case subject to customary exceptions. If the Company defaults under the loan, SVB may accelerate all of our repayment obligations and take control of our pledged assets. SVB could declare a default under the loan upon the occurrence of any event that SVB interprets as a material adverse change as defined under the loan agreement, thereby requiring us to repay the loan immediately.

As of December 31, 2018, the future contractual principal and final fee payments on our debt obligations are as follows (in thousands):

2019	$ 2,100
2020	2,800
2021	2,450
Total	$ 7,350

The following table shows actual interest expense, amortization of the debt discount and amortization of the issuance costs that was charged to interest expense (in thousands):

	For the Years Ended December 31,		
	2018	2017	2016
Stated interest	$ 479	$ 146	$ 292
Amortization of debt discount	149	44	81
Amortization of promissory notes issuance costs	56	17	—
Interest expense	$ 684	$ 207	$ 373

The Company calculated the fair value of the secured promissory notes as $6.8 million (Level 3) as of December 31, 2018. The fair value of long-term debt is based on the net present value of calculated interest and principal payments, using an interest rate of 6.75%, which takes into consideration the financial position of the Company and the recent interest rate environment for new debt issuances for comparable companies. The fair value of this equity component was derived using the Black-Scholes valuation model. The Company calculated the promissory notes' fair value by allocating to equity and the debt based on their respective fair values.

10. Shareholders' equity

Shares issued in equity sales agreement

On December 7, 2018, the Company entered into a Controlled Equity Offering[SM] Sales Agreement, or Sales Agreement, with Cantor Fitzgerald & Co., or Cantor Fitzgerald, as sales agent pursuant to which the Company may offer and sell from time to time, through Cantor Fitzgerald, common shares of the Company having an aggregate offering price of up to $20.0 million. The Company will pay Cantor Fitzgerald an amount equal to 3.0% of the aggregate gross proceeds from each sale of common shares.

As of December 31, 2018, the Company issued 94,762 commons shares at a weighted average price of $1.28 for total proceeds of $121,000.

Shares issued in public offering

On August 26, 2016, the Company completed a public offering whereby it issued 7,475,000 common shares at a price of $4.00 per share. The Company received $27.4 million, net of underwriters' discounts, commissions and offering cost.

For each common share purchased, the investors received a warrant to purchase 0.75 of a common share of the Company at an exercise price of $4.00 per full share for a period of five years from August 26, 2016. The common share warrants are recorded as a liability and then marked to market each period through earnings in other income (expense) each period as the warrants included in this transaction contain a "fundamental change" provision, which may in certain circumstances allow the common share warrants to be redeemed for cash at an amount equal to the Black-Scholes Value, as defined by the warrant agreements. In addition, the warrants include a "failure to timely deliver shares" provision, which may require the Company to pay cash to the warrant holder in certain circumstances as defined by the warrant agreements. See a discussion on the calculation of the fair value associated with these warrants at Note 5.

In connection with this offering the Company incurred offering costs of approximately $2.5 million. The Company allocated these offering costs between the estimated fair value of the common shares and the fair value of the warrants on the date of their issuance. The Company allocated approximately $1.1 million of offering costs to the common shares which was recorded as a reduction to equity. The remaining $1.4 million of offering costs was allocated to the warrants. The amount allocated to the warrants was expensed and included as a component of general and administrative expenses for the year ended December 31, 2016 as the warrants are classified as liabilities.

Shares issued in registered direct transaction

On May 11, 2016, the Company completed an offering in which net proceeds of approximately $4.6 million was raised by selling 3,571,428 common shares at a price of $1.40 per share. Additionally, for each common share purchased, the investors received a warrant to purchase one-half of a common share of the Company at an exercise price of $1.40 per full share for a period of five years from May 11, 2016. During the year ended December 31, 2016, 1,775,714 of these warrants were exercised which generated proceeds of $2.5 million. As of December 31, 2018, 10,000 of these warrants remain outstanding.

The common share warrants are recorded as a liability and then marked to market each period through earnings in other income (expense) each period as the warrants included in this transaction contain a "fundamental change" provision, which may in certain circumstances allow the common share warrants to be redeemed for cash at an amount equal to the Black-Scholes Value, as defined by the warrant agreements. In addition, the warrants include a "failure to timely deliver shares" provision, which may require the Company to pay cash to the warrant holder in certain circumstances as defined by the warrant agreements. See a discussion on the calculation of the fair value associated with these warrants at Note 5.

Authorized

As of December 31, 2018 and 2017, the Company had unlimited shares of no par common shares authorized. There were 30.2 million and 30.1 million common shares issued and outstanding as of December 31, 2018 and 2017, respectively.

Shares reserved for future issuance

The shares reserved for future issuance as of December 31, 2018, 2017 and 2016 consisted of the following (in thousands):

	December 31,		
	2018	**2017**	**2016**
Common share purchase warrants	5,798	5,825	5,965
Stock options			
Granted and outstanding	2,950	2,931	2,868
Reserved for future grants	71	36	143
	8,819	8,792	8,976

11. Common share purchase warrants

At December 31, 2018 and 2017 there were 5.8 million and 5.8 million common share purchase warrants outstanding at a weighted average exercise price of $3.94 and $4.05, respectively. During the year ended December 31, 2018, no common share purchase warrants were issued or expired.

The following table summarizes the expiration dates for the Company's outstanding common share purchase warrants as of December 31, 2018 (in thousands) except per share data:

Number of warrants outstanding	Exercise Price	Expiration date
10	$ 1.40	May 11, 2021
82	$ 2.19	June 30, 2021
5,606	$ 4.00	August 26, 2021
100	$ 2.11	September 8, 2024
5,798		

12. Stock-based compensation plan

The Company's Amended and Restated 2011 Stock Option plan, or the Plan, provides for the granting of options for the purchase of common shares of the Company at the fair value of the Company's common shares on the date of the option grant. Options are granted to employees, directors and non-employees. The board of directors or a committee appointed by the board of directors administers the Plan and has discretion as to the number, vesting period and expiry date of each option award. Historically the Company granted options with an exercise price denominated in Canadian dollars prior to the Company's U.S. IPO. Following the Company's U.S. IPO the Company has granted options with an exercise price denominated in U.S. dollars.

The Plan is based on a cumulative percentage of options issuable up to 10% of the Company's outstanding common shares. As of December 31, 2018, 2017 and 2016, there were 71,041, 35,646, and 142,566 shares, respectively, registered and unregistered available to be issued under the Plan.

During the year ended December 31, 2018, the Company issued options to purchase 1,115,667 common shares to its directors and employees. These options vest over a three year period for employees and over a one year period for directors. The contractual period for the granted options is ten years.

The Company recognized stock-based compensation expense as follows (in thousands):

	For the Years Ended December 31,		
	2018	2017	2016
Research and development	$ 177	$ 481	$ 143
General and administrative	683	1,231	282
Total	$ 860	$ 1,712	$ 425

As of December 31, 2018 there were $0.9 million of unrecognized compensation costs related to unvested stock options. As of December 31, 2018 the Company expects to recognize those costs over a weighted average period of 1.5 years.

The fair values of options granted during the year ended December 31, 2018, 2017 and 2016 were estimated at the date of grant using the following weighted-average assumptions:

	For the Years Ended December 31,		
	2018	2017	2016
Expected life of the option term (years)	4.9	4.2	3.9
Risk-free interest rate	2.5%	1.9%	1.5%
Dividend rate	0.0%	0.0%	0.0%
Volatility	127.7%	134.8%	144.0%

Expected Life of the Option Term – This is the period of time that the options granted are expected to remain unexercised. Options granted during 2018 have a contractual term of ten years. The Company estimates the expected life of the option term based on actual past behavior for similar options.

Risk-Free Interest Rate – This is the United States Treasury rates that most closely resembles the expected life of the option.

Dividend Rate – The Company has never declared or paid dividends on common shares and has no plans to do so in the foreseeable future.

Volatility – Volatility is a measure of the amount by which a financial variable such as a share price has fluctuated or is expected to fluctuate during a period. The Company considered the historical volatility from its Canadian initial public offering through the dates of grants.

The following table summarizes stock option activity, including options issued to employees, directors and non-employees (in thousands, except per share and contractual term data):

	Options Outstanding	Weighted Average Exercise Price	Weighted Average Remaining Contractual Term (in years)	Aggregate Intrinsic Value
Outstanding at January 1, 2016	1,677	$ 5.52	2.9	$ 374
Options granted	1,290	2.21		
Options exercised	(41)	2.26		
Options expired	(56)	28.94		
Options forfeited	(2)	4.41		
Outstanding at December 31, 2016	2,868	$ 3.63	4.8	$ 1,431
Options granted	222	2.12		
Options exercised	(3)	0.46		
Options expired	(101)	16.34		
Options forfeited	(55)	2.23		
Outstanding at December 31, 2017	2,931	$ 3.10	4.4	$ 992
Options granted	1,116	0.98		
Options expired	(1,097)	4.74		
Outstanding at December 31, 2018	2,950	$ 1.60	7.3	$ 83
Vested or expected to vest at December 31, 2018	2,950	$ 1.60	7.3	$ 83
Exercisable at December 31, 2018	1,431	$ 1.89	5.2	$ 83

The weighted average fair value of options granted during the years ended December 31, 2018, 2017 and 2016 was approximately $0.83, $1.78 and $1.88, respectively.

The aggregate intrinsic value was calculated as the difference between the exercise price of the stock options converted to U.S. dollars and the fair value of the Company's common stock as of the respective balance sheet date. The Company settles employee stock option exercises with newly issued common shares.

13. Revenue for license agreements

In April 2010, the Company entered into an exclusive license agreement for the development and commercialization of topsalysin (and other products covered by the licensed patent). The agreement with Kissei Pharmaceuticals Co., Ltd., a Japanese pharmaceutical company, or Kissei, covers the development and commercialization of topsalysin in Japan for the treatment of the symptoms of BPH, prostate cancer, prostatitis or other diseases of the prostate.

Pursuant to the agreement in 2010, the Company received an upfront license payment of $3.0 million. In addition to the upfront license payment, the Company was entitled to receive up to $72.0 million of non-refundable development and sales-based milestone payments as follows: a total of $17.0 million for the BPH indication, of which $5.0 million relates to the completion of certain development activities, $7.0 million relates to the completion of regulatory approvals in Japan and $5.0 million relates to the achievement of certain product sale goals in Japan; a total of $21.0 million for the prostate cancer indication, of which $7.0 million relates to the completion of certain development activities in Japan, $7.0 million relates to the completion of regulatory approvals in Japan and $7.0 million relates to the achievement of certain product sale goals in Japan; and a total of $21.0 million for prostatitis or other diseases of the prostate, of which $7.0 million relates to the completion of certain development activities in Japan, $7.0 million relates to the completion of regulatory approvals in Japan and $7.0 million relates to the achievement of certain product sale goals in Japan. An additional $13.0 million of aggregate milestone payments are not indication specific, of which $5.0 million relates to the completion of regulatory approvals and $8.0 million relates to the achievement of certain product sale goals in Japan. The Company may also receive a drug supply fee, assuming the Company supplies material to Kissei and royalty payments in the 20-29% range as a percentage of future net sales of licensed products sold under the agreement.

Accounting for the Kissei Agreement prior to the Adoption of ASC Topic 606:

The Company recognized the entire $3.0 million upfront license payment as revenue in 2010. During the year ended December 31, 2013, the Company recorded as revenue a $5.0 million non-refundable milestone payment due from Kissei upon the achievement of certain development activities. No other amounts related to this agreement have been recorded as revenue.

Accounting for the Kissei Agreement after the Adoption of Topic 606:

Effective January 1, 2018, the Company adopted ASU, No. 2014-09, "*Revenue from Contracts with Customers (Topic 606)* " and the related amendments that were issued by the FASB. Upon adoption of this standard, the Company utilized the modified retrospective adoption method, meaning that any identified cumulative effect of applying the new guidance would be recognized as an adjustment to the opening retained earnings balance.

The Company has reviewed its agreement with Kissei and determined that Kissei met the definition of a customer as defined in Topic 606. In addition, the Company confirmed that the agreement has been approved by all parties, each party's rights to goods or services to be transferred can be identified, the payment terms are defined, the contract has commercial substance and it is probable that the Company will collect substantially all of the consideration when due.

The Company determined that the license provided to Kissei represents a right to use functional intellectual property. This determination is based upon Kissei's ability to use the license as soon as it was granted and that the Company has no further obligations, as outlined in the agreement, to improve or change the licensed intellectual property. In addition, the licensed intellectual property is not expected to substantially change during the licensed period. With that being said, the agreement includes a provision whereby any improvements to the licensed intellectual property will be granted to the other party through an exclusive, fully paid, perpetual license. As this performance obligation was completed upon the transfer of the license, and given there are no additional performance obligations under the terms of the agreement, there is no impact upon adoption on the $3.0 million upfront license recognized as revenue in 2010.

As outlined above the agreement also includes development and sales-based milestone payments and sales-based royalties. Upon the signing of the agreement, the development based milestone payments would have been considered variable consideration under Topic 606 as the payment of these milestones was contingent upon actions of Kissei or other third parties or were based upon the successful outcome of clinical trials or other development activities performed by the Company. Variable consideration is subject to a constraint which limits the amount of variable consideration which can be included in the transaction price to the amount which is probable to not be reversed when the uncertainty associated with the variable consideration is subsequently resolved. At each future reporting date the Company reassesses the constraint applied to each unrecognized development based milestone. To the extent that an uncertainty is no longer identified the Company may recognize all or a portion of a development based milestone assuming no other factors relating to the ultimate payment of the development milestone are identified. The recognition of revenue for the $5.0 million development milestone payment upon the achievement of certain development activities during the year ended December 31, 2013 would be appropriate under Topic 606 and therefore there is no impact upon adoption on the $5.0 million development milestone payment recognized as revenue in 2013.

Topic 606 includes an exception for the recognition of revenue relating to licenses of intellectual property with sales- or usage-based royalties whereby sales-based milestone payments and sales-based royalties will not be recognized as revenue until the later of the following events occur: the subsequent sale occurs or the performance obligation to which some or all of the sales based royalty has been allocated has been satisfied. Accordingly, there is no impact upon adoption as no revenue has historically been recorded related to these items.

Based on the above, the Company's adoption of Topic 606 did not have an impact on the Company's historical financial statements and therefore no adjustments were required to the Company's financial statements as a result of the adoption of Topic 606.

14. Income taxes

The component of the loss before provision for income taxes were as follows (in thousands):

	For the Years Ended December 31,		
	2018	2017	2016
United States	$ (623)	$ (1,931)	$ (521)
Canada	(6,155)	(6,697)	(10,643)
Loss before provision for income taxes	$ (6,778)	$ (8,628)	$ (11,164)

The components of the provision for income taxes from continuing operations is as follows (in thousands):

	For the Years Ended December 31,		
	2018	2017	2016
Current Tax:			
Canada	$ —	$ —	$ —
US	—	—	—
State	—	—	—
	$ —	$ —	$ —
Deferred Tax:			
Canada	$ —	$ —	$ —
US	—	—	—
State	—	—	—
	—	—	—
	$ —	$ —	$ —

A reconciliation of income taxes to the amount computed by applying the statutory federal income tax rate to the net loss is as follows (in thousands, except income tax rates):

	For the Years Ended December 31,		
	2018	2017	2016
Combined federal and provincial income tax rates	27.00%	26.00%	26.00%
Income tax benefit at statutory rates	$ (1,830)	$ (2,243)	$ (2,902)
State income tax, net of federal benefit	22	(3)	1
Permanent items	2	3	(17)
Tax credits	(144)	—	—
Non-deductible stock-based compensation	552	429	81
Foreign accrual property income	120	72	69
Expired NOLs	200	140	79
Return to provision true up	39	1	60
Uncertain tax positions	15	718	68
Rate differential	57	(154)	60
Effect of Canadian rate change	—	(1,428)	—
Effect of U.S. federal rate change	—	545	—
Effect of U.S. state rate change	(18)	—	183
Other	31	12	(112)
Revaluation of warrant liability	(2,346)	(860)	86
CTA	—	—	(312)
Change in valuation allowance	3,300	2,768	2,656
Income tax expense	$ —	$ —	$ —

Significant components of the Company's deferred tax assets as of December 31, 2018 and 2017 are shown below (in thousands):

	December 31,	
	2018	2017
Deferred tax assets:		
Net operating loss carryforwards (non-capital losses)	$ 40,169	$ 36,110
Scientific research and development	2,605	2,605
Tax credits	3,889	3,964
Stock based compensation	410	815
Other, net	63	164
Share issue costs	344	490
Total deferred tax assets, net, before valuation allowance	47,480	44,148
Valuation allowance	(47,480)	(44,148)
Net deferred tax assets	$ —	$ —

Due to the operating losses since inception, a valuation allowance has been recognized to offset net deferred tax assets as realization of such deferred tax assets is not more likely than not. During the years ended December 31, 2018 and 2017, the valuation allowance on the deferred tax assets increased by $3.3 million and $2.7 million, respectively.

At December 31, 2018, the Company had Canadian, U.S. federal and California net operating loss carryforwards of approximately $148.4 million, $2.5 million and $1.5 million, respectively, which may be used to reduce future taxable income. The income tax benefit, if any, of these losses has not been recorded due to the uncertainty of their recovery. The net operating losses being to expire in 2026 for Canadian tax purposes, 2034 for U.S. federal tax purposes and 2034 for California tax purposes. As a result of tax reform enacted in 2017, U.S. federal net operating losses generated in 2018 and forward will be carried forward indefinitely and be available to offset up to 80% of future taxable income each year.

At December 31, 2018, the Company had Canadian Scientific Research and Experimental Development, or SR&ED, tax credits, investment tax credits and foreign tax credits of approximately $9.6 million, $2.4 million and $0.2 million. The SR&ED tax credits carry forward indefinitely, while the investment tax credits and foreign tax credits begin to expire in 2019 and 2023, respectively.

In addition, the Company has U.S. federal and California research and development tax credits of $1.7 million and $0.6 million. The federal credits begin to expire in 2031 and the California credits carry forward indefinitely.

The Company's Canadian tax years are subject to inspection from 2011 forward. The Company's U.S. federal and California 2011 tax returns are subject to examination by taxing authorities.

The future utilization of the Company's net operating loss carry forwards and research and development credit carry forwards to offset future taxable income and tax, respectively, may be subject to an annual limitation under Internal Revenue Code of 1986, as amended, or the Code, Sections 382 and 383 as a result of ownership changes that may have occurred previously or may occur in the future. Section 382 and 383 limits a company's ability to utilize certain net operating loss carry forwards and tax credit carry forwards in the event of a cumulative change in ownerships in excess of 50% as defined in the Code.

Uncertain Tax Positions

In accordance with ASC740, "*Income Taxes*" (ASC740), tax benefits. In accordance with ASC740, tax benefits are only recognized when a position is more likely than not of being sustained. Tax benefits are then measured using a cumulative benefit approach whereby the largest amount of tax benefit that is more likely than not of being sustained is recognized.

The following table summarizes the activity related to the Company's unrecognized tax benefits (in thousands):

	For the Years Ended December 31,		
	2018	**2017**	**2016**
Beginning balance	$ 1,151	$ 428	$ 325
Increase related to prior year tax positions	—	610	103
Increase related to current year tax positions	22	113	—
Ending balance	$ 1,173	$ 1,151	$ 428

The amount of unrecognized tax benefit that, if recognized and realized, would affect the effective tax rate is zero as of December 31, 2018. To the extent unrecognized tax benefits are recognized at a time such valuation allowance no longer exists, the addition amount that would affect the effective tax rate is approximately $1.2 million. The Company does not anticipate any significant decreases in its unrecognized tax benefits over the next 12 months. The Company recognizes interest and/or penalties related to income tax matters in income tax expense. For the years ended December 31, 2018 and 2017, the Company has not recognized any interest or penalties related to income taxes.

The Tax Cuts and Jobs Act or Tax Act, which was enacted on December 22, 2017, reduced the U.S. federal corporate tax rate from 35% to 21% and repealed the corporate Alternative Minimum Tax. As a result of the Tax Act, the Company remeasured certain deferred tax assets and liabilities based on the rates at which they are expected to reverse in the future, which is generally 21%. The amount recorded related to the remeasurement of the Company's deferred tax balance was $0.5 million, which was fully offset by a decrease in the Company's valuation allowance and resulted in no impact to income tax expense.

In conjunction with the tax law change, the Securities and Exchange Commission staff issued Staff Accounting Bulletin No. 118 to address the application of GAAP in situations when a registrant does not have the necessary information available, prepared, or analyzed (including computations) in reasonable detail to complete the accounting for certain income tax effects of the Tax Act. At December 31, 2018, the Company has now completed its accounting for the income tax effects of the Tax Act and recognized no adjustments to the provisional amounts recorded at December 31, 2017.

On September 11, 2017, British Columbia's Minister of Finance, presented the New Democratic Party's first provincial budget. The budget increased the general and manufacturing and processing (M&P) income tax rate for British Columbia from 11% to 12% effective January 1, 2018 and the combined federal and British Columbia rate increased from 26% to 27%. As a result of the change in the income tax rate, the Company remeasured certain deferred tax assets and liabilities based on the rate at which they are expected to be reverse in the future, which is generally 27%. The amount recorded related to the remeasurment of our deferred tax balance was $1.4 million. The corresponding increase in valuation allowance resulted in an income tax benefit.

15. Commitments and contingencies

Operating leases

The Company leases a facility, comprising the Company's headquarters, located in San Diego, California under a non-cancelable lease. During January 2019, the Company exercised a one-year lease extension on its headquarters in San Diego, California. As a result of this extension, the expiration date for the Company's headquarters was extended from May 2019 to May 2020. The rent on the Company's headquarters is currently $9,517 per month.

Total rent expense under operating leases was $0.1 million for the years ended December 31, 2018, 2017 and 2016, respectively.

Future minimum lease payments under non-cancelable operating leases at December 31, 2018 are as follows (in thousands):

	Future rent payments
2019	$ 130
2020	54
Total	$ 184

Purchase commitments

The Company is required to schedule its manufacturing activities in advance. If the Company cancels any of these scheduled activities without proper notice the Company would be required to pay penalties equal to the cost of the originally scheduled activity. The Company estimates that the cost of these penalties would be approximately $0.7 million at December 31, 2018 if the Company cancels the scheduled activities. The amounts recorded under these manufacturing contracts included in research and development was $4.8 million, $0.6 million and $0.3 million for the years ended December 31, 2018, 2017 and 2016, respectively.

License agreements

Topsalysin License Agreement for Prostate Cancer

In 2004, the Company licensed exclusive rights to topsalysin for the treatment of prostate cancer under an agreement with UVIC and Johns Hopkins. The Company has agreed to make cumulative milestone payments over the lifecycle of topsalysin of up to CND$3.6 million, or $2.6 million, as converted, on the achievement of certain clinical and regulatory milestones and to pay royalties on commercial sales of resulting products. From the inception of the agreement, we have paid milestone payments of CND$0.1 million, or $0.1 million, applying the historical conversion rate at each payment date. To date the Company has completed three clinical trials in patients with prostate cancer.

Topsalysin License Agreement for BPH

In 2009, the Company licensed exclusive rights to topsalysin under an agreement with UVIC and Johns Hopkins with respect to the use of topsalysin for the treatment of the symptoms of BPH and other non-cancer diseases and conditions of the prostate, with the exception of prostate cancer. The license agreement requires us to make payments of CND$1.3 million, or $1.0 million, as converted, on the achievement of certain clinical and regulatory milestones and to pay royalties on commercial sales of resulting products. From the inception of the agreement, the Company has incurred sub-license fees of $0.6 million and milestone payments of $0.1 million under this agreement.

As the timing of when these payments will actually be made is uncertain and the payments are contingent upon the completion of future events, the Company cannot predict minimum future payments over the next five years.

16. 401(k) plan

The Company has a deferred compensation plan, or the 401(k) Plan, pursuant to Section 401(k) of the Code where by all employees, subject to certain age requirement can contribute pretax earnings to the plan. The Company makes safe harbor contributions to the 401(k) Plan up to 4% of eligible compensation, subject to limitations under the Code. The Company's total contributions to the 401(k) Plan were $0.1 million for each of the years ended December 31, 2018, 2017 and 2016.

Item 9. Changes in and Disagreements with Accountants on Accounting and Financial Disclosures

None.

Item 9A. Controls and Procedures

Evaluation of Disclosure Controls and Procedures

We maintain disclosure controls and procedures that are designed to provide reasonable assurance that information required to be disclosed in the reports that we file or submit to the SEC under the Exchange Act 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 chief executive officer and chief financial officer, as appropriate, to allow timely decisions regarding required disclosure. In designing and evaluating the disclosure controls and procedures, management recognized 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 necessarily was 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, control 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 chief executive officer and chief 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 Exchange Act. Based on this evaluation, our chief executive officer and chief 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 is defined in Exchange Act Rules 13a-15(f) and 15d-15(f). Internal control over financial reporting is a process designed under the supervision and with the participation of our management, including our chief executive officer and chief financial officer, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles.

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.

The effectiveness of our internal control over financial reporting as of December 31, 2018 has been audited by PricewaterhouseCoopers LLP, an independent registered public accounting firm, as stated in its report, which is included herein.

Changes in Internal Control Over Financial Reporting

There were no changes in our internal control over financial reporting identified in management's evaluation pursuant to Rules 13a-15(d) or 15d-15(d) of the Exchange Act during the quarter ended December 31, 2018 that materially affected, or are reasonably likely to materially affect, our internal control over financial reporting.

Item 9B. Other Information

Not applicable.

Part III.

Certain information required by Part III of this Annual Report on Form 10-K is omitted from this report because the registrant will file a definitive Proxy Statement within 120 days after the end of its fiscal year pursuant to Regulation 14A for its 2019 Annual Meeting of Shareholders to be held within 180 days of December 31, 2018, referred to as the Proxy Statement, and the information included therein is incorporated herein by reference.

Item 10. Directors, Executive Officers and Corporate Governance

The information required by this item is incorporated herein by reference to the information from the Proxy Statement under the sections entitled "Election of Directors" "Executive Officers" and "Section 16(a) Beneficial Ownership Reporting Compliance."

We have adopted a code of ethics for directors, officers (including our principal executive officer, principal financial officer and principal accounting officer) and employees, known as the Code of Business Conduct and Ethics. The Code of Business Conduct and Ethics is available on our website at http://www.sophirisbio.com under the Corporate Governance section of our Investor Relations page. We will promptly disclose on our website (i) the nature of any amendment to the policy that applies to our principal executive officer, principal financial officer, principal accounting officer or controller, or persons performing similar functions and (ii) the nature of any waiver, including an implicit waiver, from a provision of the policy that is granted to one of these specified individuals that is required to be disclosed pursuant to SEC rules and regulations, the name of such person who is granted the waiver and the date of the waiver.

Item 11. Executive Compensation

The information required by this item is incorporated herein by reference to the information from the Proxy Statement under the sections entitled "Executive and Director Compensation" and "Compensation Committee Interlocks and Insider Participation."

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

The information required by this item is incorporated herein by reference to the information from the Proxy Statement under the sections entitled "Principal Shareholders" and "Equity Compensation Plan Information."

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

The information required by this item is incorporated herein by reference to the information from the Proxy Statement under the sections entitled "Election of Directors" and "Certain Relationships and Related Party Transactions."

Item 14. Principal Accounting Fees and Services

The information required by this item is incorporated herein by reference to the information from the Proxy Statement under the section entitled "Principal Accountant Fees and Services" and "Pre-Approval Policies and Procedures."

Part IV.

Item 15. Exhibits, Financial Statements and Schedules

(a) Documents filed as part of this report.

1. *Financial Statements.* We have filed the following documents as part of this Annual Report:

2. *Financial Statement Schedules.*

All schedules are omitted because they are not applicable or the required information is shown in the Financial Statements or notes thereto.

(b) *Exhibits*

The following exhibits are filed as part of, or incorporated by reference into, this report:

Exhibit number	Description of Exhibit	Incorporated by Reference or Attached Hereto
3.1	Certificate of Amalgamation of the Registrant, dated January 1, 2005.	Incorporated by reference to the Registrant's Form S-1 (SEC File No. 333-186724) filed on February 15, 2013.
3.2	Notice of Articles of the Registrant.	Incorporated by reference to the Quarterly Report on Form 10-Q filed on August 10, 2017.
3.3	Articles of the Registrant.	Incorporated by reference to the Registrant's Form S-1 (SEC File No. 333-186724) filed on February 15, 2013.
4.1	Form of Common Share Certificate.	Incorporated by reference to the Amendment No. 4 to the Registrant's Form S-1/A (SEC File No. 333-186724) filed on July 15, 2013.
4.2	Common Share Purchase Warrant Issued to Oxford Finance LLC dated June 30, 2014.	Incorporated by reference to the Quarterly Report on Form 10-Q filed on August 7, 2014.
4.3	Common Share Purchase Warrant Issued to Oxford Finance LLC dated June 30, 2014.	Incorporated by reference to the Quarterly Report on Form 10-Q filed on August 7, 2014.
4.4	Form of Common Share Purchase Warrant Issued in connection with the Company's May 2016 Financing.	Incorporated by reference to the Current Report on Form 8-K filed on May 11, 2016.
4.5	Form of Common Share Purchase Warrant Issued in connection with the Company's August 2016 Financing.	Incorporated by reference to the Current Report on Form 8-K filed on August 23, 2016.
4. 6	Common Share Purchase Warrant Issued to Silicon Valley Bank, dated September 8, 2017.	Incorporated by reference to the Quarterly Report on Form 10-Q filed on November 9, 2017.
10.1+	Amended and Restated 2011 Stock Option Plan.	Incorporated by reference to the Registrant's Form S-1 (SEC File No. 333-186724) filed on February 15, 2013.

10.2+	Form of Option Certificate.	Incorporated by reference to the Registrant's Form S-1 (SEC File No. 333-186724) filed on February 15, 2013.
10.3+	Form of Indemnification Agreement by and between the Company and each of its directors.	Incorporated by reference to the Registrant's Form S-1 (SEC File No. 333-186724) filed on February 15, 2013.
10.4+	Employment Agreement by and between Sophiris Bio Corp. and Allison Hulme, Ph.D., dated March 31, 2011.	Incorporated by reference to the Registrant's Form S-1 (SEC File No. 333-186724) filed on February 15, 2013.
10.5+	Employment Agreement between Sophiris Bio Corp. and Randall E. Woods, dated August 16, 2012.	Incorporated by reference to the Registrant's Form S-1 (SEC File No. 333-186724) filed on February 15, 2013.
10.6+	Employment Agreement between Sophiris Bio Corp. and Peter Slover, dated March 19, 2012.	Incorporated by reference to the Registrant's Form S-1 (SEC File No. 333-186724) filed on February 15, 2013.
10.7*	Exclusive License Agreement effective September 30, 2004 by and among UVIC Industry Partnerships Inc., The Johns Hopkins University and the Registrant.	Incorporated by reference to the Registrant's Form S-1 (SEC File No. 333-186724) filed on February 15, 2013.
10.8	Amendment to Exclusive License Agreement by and among UVIC Industry Partnerships Inc., The Johns Hopkins University and the Registrant, dated January 10, 2005.	Incorporated by reference to the Registrant's Form S-1 (SEC File No. 333-186724) filed on February 15, 2013.
10.9*	Exclusive License Agreement effective October 16, 2009 by and among UVIC Industry Partnerships Inc., The Johns Hopkins University and the Registrant.	Incorporated by reference to the Registrant's Form S-1 (SEC File No. 333-186724) filed on February 15, 2013.
10.10*	Exclusive License Agreement by and between the Registrant and Kissei Pharmaceuticals Co., Ltd., dated April 28, 2010.	Incorporated by reference to the Registrant's Form S-1 (SEC File No. 333-186724) filed on February 15, 2013.
10.11	Exclusive License Amending Agreement by and among UVIC Industry Partnerships Inc., The Johns Hopkins University and the Registrant, dated July 1, 2010, with respect to the Exclusive License Agreement effective September 30, 2004 by and among UVIC Industry Partnerships Inc., The Johns Hopkins University and the Registrant.	Incorporated by reference to the Registrant's Form S-1 (SEC File No. 333-186724) filed on February 15, 2013.
10.12	Exclusive License Amending Agreement by and among UVIC Industry Partnerships Inc., The Johns Hopkins University and the Registrant, dated July 1, 2010, with respect to the Exclusive License Agreement effective October 16, 2009 by and among UVIC Industry Partnerships Inc., The Johns Hopkins University and the Registrant.	Incorporated by reference to the Registrant's Form S-1 (SEC File No. 333-186724) filed on February 15, 2013.
10.13	Standard Lease by and between Allison-Zongker, L.P. and the Registrant, dated April 15, 2011.	Incorporated by reference to the Registrant's Form S-1 (SEC File No. 333-186724) filed on February 15, 2013.
10.14	First Amendment to that Certain Lease Agreement dated April 15, 2011 by and between Allison-Zongker, L.P. and the Registrant, effective April 2, 2012.	Incorporated by reference to the Registrant's Form S-1 (SEC File No. 333-186724) filed on February 15, 2013.
10.15	Indemnification Letter Agreement by and between the Registrant, Warburg Pincus Private Equity X, L.P. and Warburg Pincus X Partners, L.P., dated November 19, 2010.	Incorporated by reference to the Registrant's Form S-1 (SEC File No. 333-186724) filed on February 15, 2013.
10.16*	Technology Transfer and Supply Agreement by and between Boehringer Ingelheim RCV GmbH & Co KG and the Registrant, dated June 29, 2012.	Incorporated by reference to the Registrant's Form S-1 (SEC File No. 333-186724) filed on February 15, 2013.

10.17+	Non-employee Director Compensation Program.	Incorporated by reference to the Current Report on Form 8-K filed on March 17, 2017.
10.18	Agreement Respecting Intellectual Property by and between the Registrant and Dr. J. Thomas Buckley, dated February 12, 2003, as amended by the Amendment Agreement dated May 5, 2004.	Incorporated by reference to the Amendment No. 4 to the Registrant's Form S-1/A (SEC File No. 333-186724) filed on July 15, 2013.
10.19+	Officer Change in Control Severance Benefit Agreement by and between Randall E. Woods and the Registrant.	Incorporated by reference to the Quarterly Report on Form 10-Q filed on November 12, 2014.
10.20+	Officer Change in Control Severance Benefit Agreement by and between Allison Hulme and the Registrant.	Incorporated by reference to the Quarterly Report on Form 10-Q filed on November 12, 2014.
10.21+	Officer Change in Control Severance Benefit Agreement by and between Peter T. Slover and the Company.	Incorporated by reference to the Quarterly Report on Form 10-Q filed on November 12, 2014.
10.22	Loan and Security Agreement, dated September 8, 2017 by and among the Registrant, Sophiris Bio Corp., Sophiris Bio Holding Corp. and Silicon Valley Bank.	Incorporated by reference to the Quarterly Report on Form 10-Q filed on November 9, 2017.
10.23	Controlled Equity Offering℠ Sales Agreement dated December 7, 2018 by and among the Registrant and Cantor Fitzgerald & Co.	Incorporated by reference to the Current Report on Form 8-K filed on December 7, 2018.
23.1	Consent of Independent Registered Public Accounting Firm.	Attached hereto
24.1	Power of Attorney (included on signature page).	Attached hereto
31.1	Certification of Chief Executive Officer pursuant to Rules 13a-14 and 15d-14 promulgated pursuant to the Securities Exchange Act of 1934, as amended.	Attached hereto
31.2	Certification of Chief Financial Officer pursuant to Rules 13a-14 and 15d-14 promulgated pursuant to the Securities Exchange Act of 1934, as amended.	Attached hereto
32.1	Certification of Chief Executive Officer pursuant to Section 906 of the Sarbanes-Oxley Act of 2002.	Attached hereto
32.2	Certification of Chief Financial Officer pursuant to Section 906 of the Sarbanes-Oxley Act of 2002.	Attached hereto
101.INS**	XBRL Instance Document	Attached hereto
101.SCH**	XBRL Taxonomy Extension Schema Document	Attached hereto
101.CAL**	XBRL Taxonomy Extension Calculation Linkbase Document	Attached hereto
101.DEF**	XBRL Taxonomy Extension Definition Linkbase Document	Attached hereto
101.LAB**	XBRL Taxonomy Extension Label Linkbase Document	Attached hereto
101.PRE**	XBRL Taxonomy Extension Presentation Linkbase Document	Attached hereto

+ 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.

** In accordance with Rule 406T of Regulation S-T, the XBRL related information in Exhibit 101 to this Annual Report on Form 10-K is deemed not filed or part of a registration statement or prospectus for purposes of Sections 11 or 12 of the Securities Act, is deemed not filed for purposes of Section 18 of the Exchange Act, and otherwise is not subject to liability under these sections.

Item 16. Form 10-K Summary

None.

SIGNATURES

Pursuant to the requirements of the Securities Act, the Registrant has duly caused this report to be signed on its behalf by the undersigned, thereunto duly authorized, in the City of San Diego, State of California, on the 13th day of March 2019.

SOPHIRIS BIO INC.

By: /s/ Randall E. Woods
Randall E. Woods
Chief Executive Officer and President

KNOW ALL PERSONS BY THESE PRESENTS, that each person whose signature appears below constitutes and appoints Randall E. Woods and Peter T. Slover, and each of them, his or her true and lawful attorneys-in-fact and agents, with full power of substitution and resubstitution, for him or her and in his or her name, place and stead, in any and all capacities, to sign any and all amendments (including post-effective amendments) to this report, and to file the same, with all exhibits thereto, and other documents in connection therewith, with the Securities and Exchange Commission, granting unto said attorneys-in-fact and agents, and each of them, full power and authority to do and perform each and every act and thing requisite and necessary to be done in connection therewith, as fully to all intents and purposes as he or she might or could do in person, hereby ratifying and confirming all that said attorneys-in-fact and agents, or either of them, or their or his substitutes or substitute, may lawfully do or cause to be done by virtue hereof.

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

Signature	Title	Date
/s/ Randall E. Woods Randall E. Woods	Chief Executive Officer, President and Director (Principal Executive Officer)	March 13, 2019
/s/ Peter T. Slover Peter T. Slover	Chief Financial Officer (Principal Financial Officer and Principal Accounting Officer)	March 13, 2019
/s/ Lars Ekman, M.D., Ph.D. Lars Ekman, M.D., Ph.D.	Executive Chairman and Director	March 13, 2019
/s/ Allison Hulme, Ph.D. Allison Hulme, Ph.D.	Chief Operating Officer and Director	March 13, 2019
/s/ John Geltosky, Ph.D. John Geltosky, Ph.D.	Director	March 13, 2019
/s/ Jim Heppell Jim Heppell	Director	March 13, 2019
/s/ Gerald Proehl Gerald Proehl	Director	March 13, 2019

Exhibit 23.1

CONSENT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

We hereby consent to the incorporation by reference in the Registration Statements on Form S-3 (No. 333-219887) and Form S-8 (Nos. 333-190945, 333-203136, 333-210452, 333-211814 and 333-215227) of Sophiris Bio Inc. of our report dated March 13, 2019 relating to the financial statements and the effectiveness of internal control over financial reporting, which appears in this Form 10-K.

/s/ PricewaterhouseCoopers LLP
San Diego, California
March 13, 2019

Exhibit 31.1

CERTIFICATION OF PRINCIPAL EXECUTIVE OFFICER
PURSUANT TO SECTION 302 OF THE SARBANES-OXLEY ACT OF 2002

I, Randall E. Woods, certify that:

1. I have reviewed this annual report on Form 10-K for the fiscal year ended December 31, 2018 of Sophiris Bio Inc.;

2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;

3. Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this report;

4. The registrant's other certifying officer and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:

a.) Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;

b.) Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;

c.) Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and

d.) Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and

5. The registrant's other certifying officer and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of the registrant's board of directors (or persons performing the equivalent functions):

a.) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and

b.) Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

/s/ Randall E. Woods
Randall E. Woods
President & Chief Executive Officer

Date: March 13, 2019

Exhibit 31.2

CERTIFICATION OF PRINCIPAL FINANCIAL OFFICER
PURSUANT TO SECTION 302 OF THE SARBANES-OXLEY ACT OF 2002

I, Peter T. Slover, certify that:

1. I have reviewed this annual report on Form 10-K for the fiscal year ended December 31, 2018 of Sophiris Bio Inc.;

2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;

3. Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this report;

4. The registrant's other certifying officer and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:

a.) Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;

b.) Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;

c.) Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and

d.) Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and

5. The registrant's other certifying officer and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of the registrant's board of directors (or persons performing the equivalent functions):

a.) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and

b.) Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

/s/ Peter T. Slover
Peter T. Slover
Chief Financial Officer

Date: March 13, 2019

Exhibit 32.1

CERTIFICATION PURSUANT TO 18 U.S.C. SECTION 1350,
AS ADOPTED PURSUANT TO
SECTION 906 OF THE SARBANES-OXLEY ACT OF 2002

In connection with the annual report on Form 10-K of Sophiris Bio Inc. (the Company) for the year ended December 31, 2018 as filed with the Securities and Exchange Commission on the date hereof (the Report), I, Randall E. Woods, President and Chief Executive Officer of the Company, certify, pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002, that to my knowledge:

1. The Report fully complies with the requirements of Section 13(a) or 15(d), as applicable, of the Securities Exchange Act of 1934, as amended; and

2. The information contained in the Report fairly presents, in all material respects, the financial condition and results of operations of the Company.

/s/ Randall E. Woods
Randall E. Woods
President & Chief Executive Officer

Date: March 13, 2019

The foregoing certification is being furnished solely pursuant to 18 U.S.C. Section 1350 and is not to be incorporated by reference into any filing of the Company, whether made before or after the date hereof, regardless of any general incorporation language in such filing.

Exhibit 32.2

CERTIFICATION PURSUANT TO 18 U.S.C. SECTION 1350,
AS ADOPTED PURSUANT TO
SECTION 906 OF THE SARBANES-OXLEY ACT OF 2002

In connection with the annual report on Form 10-K of Sophiris Bio Inc. (the Company) for the year ended December 31, 2018, as filed with the Securities and Exchange Commission on the date hereof (the Report), I, Peter T. Slover, Chief Financial Officer of the Company, certify, pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002, that, to my knowledge:

1. The Report fully complies with the requirements of Section 13(a) or 15(d), as applicable, of the Securities Exchange Act of 1934, as amended; and

2. The information contained in the Report fairly presents, in all material respects, the financial condition and results of operations of the Company.

/s/ Peter T. Slover
Peter T. Slover
Chief Financial Officer

Date: March 13, 2019

The foregoing certification is being furnished solely pursuant to 18 U.S.C. Section 1350 and is not to be incorporated by reference into any filing of the Company, whether made before or after the date hereof, regardless of any general incorporation language in such filing.