

UNITED STATES

SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

Form 10-K

(Mark one)

- ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**
For the fiscal year ended December 31, 2018
- OR**
- TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**
For the transition period from to

Commission file number: 000-24477

DIFFUSION PHARMACEUTICALS INC.

(Exact Name of Registrant as specified in its Charter)

Delaware

(State or Other Jurisdiction of Incorporation or Organization)

1317 Carlton Avenue, Suite 200

Charlottesville, VA

(Address of Principal Executive Offices)

30-0645032

(I.R.S. Employer Identification No)

22902

(Zip Code)

(434) 220-0718

(Registrant's telephone number, including area code)

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

Title of Each Class	Name of Each Exchange on Which Registered
Common Stock, par value \$0.001 per share	Nasdaq Capital Market

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

None

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

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

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

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

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

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

Large accelerated filer

Non-accelerated filer

Accelerated filer

Smaller reporting company

Emerging growth company

If an emerging growth company, indicate by check mark if the registrant has elected 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 Act). Yes No

The aggregate market value of the registrant's common stock, excluding shares beneficially owned by affiliates, computed by reference to the closing sale price at which the common stock was last sold as of June 30, 2018 (the last business day of the registrant's second fiscal quarter) as quoted on the Nasdaq Capital Market on that date was approximately \$25.3 million.

As of March 13, 2019, 3,379,345 shares of common stock of the registrant were outstanding.

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This annual report on Form 10-K contains certain forward-looking statements within the meaning of Section 27A of the Securities Act of 1933, as amended, and Section 21E of the Securities Exchange Act of 1934, as amended, and are subject to the safe harbor created by those sections. For more information, see “Part I. Item 1. Business — Cautionary Note Regarding Forward-Looking Statements.”

Except as otherwise noted, references to “common stock” in this report refer to common stock, par value \$0.001 per share, of the Company.

This report contains the following trademarks, trade names and service marks of ours: Diffusion. All other trade names, trademarks and service marks appearing in this Annual Report on Form 10-K are the property of their respective owners. We have assumed that the reader understands that all such terms are source-indicating. Accordingly, such terms appear without the trade name, trademark or service mark notice for convenience only and should not be construed as being used in a descriptive or generic sense.

PART I

ITEM 1. BUSINESS

We are a clinical stage biotechnology company developing new treatments for life threatening conditions by improving the body's ability to bring oxygen to the areas where it is needed most. We are developing our lead product candidate, transcrocetinate sodium, also known as trans sodium crocetinate ("TSC"), for use in those life threatening conditions in which cellular oxygen deprivation ("hypoxia") is the basis for significant unmet medical needs. TSC is designed to safely and selectively target and re-oxygenate the micro-environment of hypoxic cells, and potentially be used in many indications, including oncology and cardiovascular/stroke. In cancer, TSC re-oxygenates treatment-resistant cancerous tissue, making the cancer cells up to three times more susceptible to the therapeutic effects of standard-of-care radiation therapy and chemotherapy. In stroke, TSC helps promote the diffusion of oxygen into those brain cells in which oxygen-deprivation causes neuronal death resulting in patient mortality or morbidity.

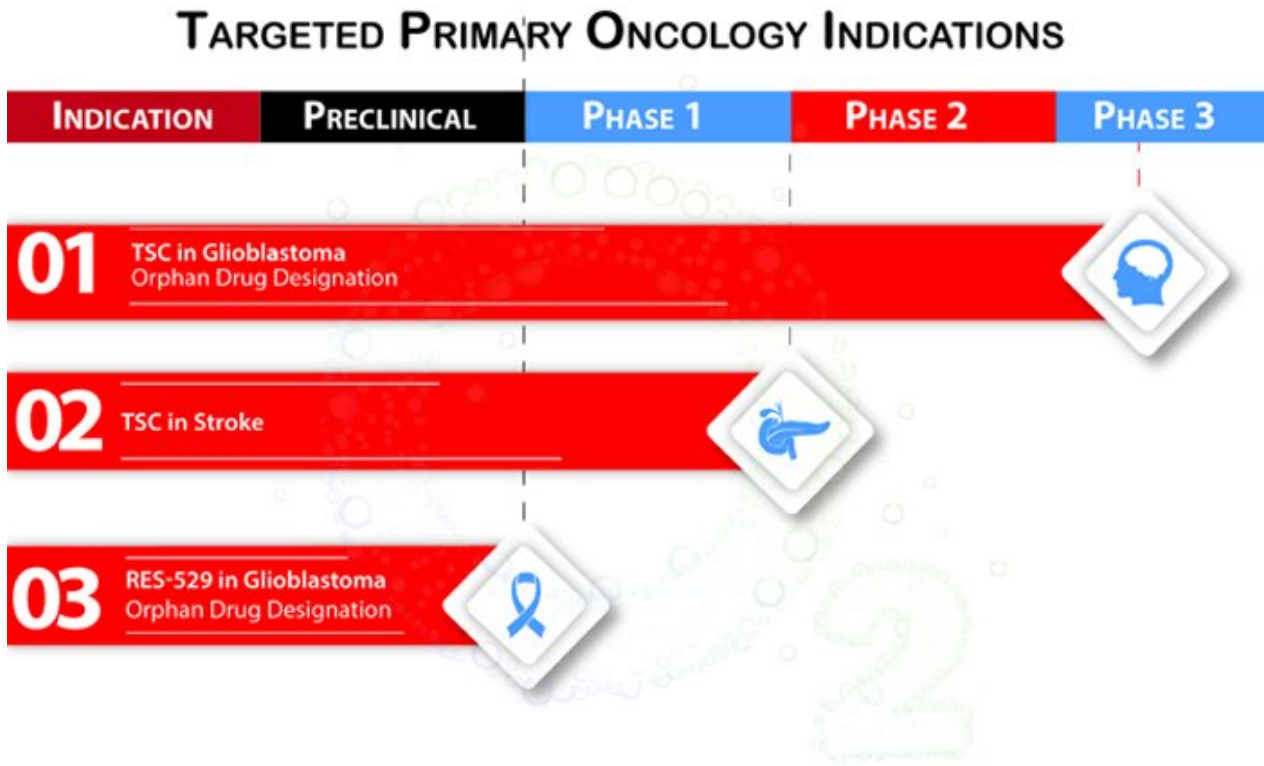
A range of tissue types, including both cancerous and normal cells, has been shown to be safely re-oxygenated in our preclinical and clinical studies using TSC's novel mechanism of action. In oncology, we believe TSC's therapeutic potential is not limited to one specific tumor type, thereby making it potentially useful to improve standard-of-care treatments in many life-threatening cancers. Given TSC's safety profile and animal data, we could, with appropriate funding, move directly into Phase 2 studies in many such cancers. Likewise, we believe TSC's ability to re-oxygenate normal tissue that has become oxygen-deprived provides opportunities for new therapeutic approaches to conditions ranging from stroke and emergency medicine to cardiovascular indications. The successful completion of trials for TSC or any other potential product candidate in these or any other indication are dependent upon our ability to further raise necessary capital.

Our most advanced program targets TSC against treatment-resistant brain cancer. A Phase 2 clinical program, completed in the second quarter of 2015, evaluated 59 patients with newly diagnosed glioblastoma multiforme ("GBM"), a particularly deadly form of primary brain cancer. This open label, historically controlled study demonstrated a favorable safety and efficacy profile for TSC when combined with GBM's standard of care, including a 37% improvement in overall survival over the control group at two years. A particularly strong efficacy signal was seen in the inoperable patients, where survival of TSC-treated patients at two years was increased by almost four-fold over the controls. In December 2017, we initiated the IN vestigation of TSC AgainstCancerousTumors (INTACT) Phase 3 trial in the newly diagnosed inoperable GBM patient population. Patient enrollment began in January 2018. The trial will enroll 236 patients in total, with 118 in the treatment arm and 118 in the control arm. The trial is beginning with an 8 patient safety run-in which the Company expects to be finished in the second quarter of 2019.

We believe that TSC has potential application in other indications involving hypoxia, notably stroke and emergency medicine, as well as cardiovascular and neurodegenerative diseases. A Phase 2 trial program in cooperation with UCLA and the University of Virginia to test TSC in the treatment of acute stroke has received approval for enrollment by the FDA, with the first enrolled patient expected in Q2 2019. This trial, which will feature in-ambulance dosing of TSC, is named the PreHospitalAcuteStrokeTherapy - TSC (PHAST - TSC) and is expected to enroll 160 patients, with 80 in the treatment arm and 80 in the control arm. We believe in-ambulance dosing of TSC could significantly cut the time in which the stroke-related oxygen deprivation to brain cells goes untreated, potentially leading to a better outcome for stroke victims treated in this manner. In the last quarter of 2018, we received FDA permission to begin patient enrollment in the PHAST - TSC Phase 2 trial and expect to begin enrollment so in second quarter 2019, following completion of institutional review board and contracting activities.

In addition to the TSC programs, we are exploring alternatives regarding how best to capitalize upon our product candidate RES-529, which may include possible out-licensing and other options. RES-529 is a novel PI3K/Akt/mTOR pathway inhibitor which has completed two Phase 1 clinical trials for age-related macular degeneration and was in preclinical development in oncology, specifically GBM. RES-529 has shown activity in both in vitro and in vivo glioblastoma animal models and has been demonstrated to be orally bioavailable and capable of crossing the blood brain barrier.

The following table, as of December 31, 2018, summarizes the planned clinical indications for Diffusion’s lead molecule, TSC and RES-529:



Technology Overview

In oncology, our proprietary technology is targeted at overcoming treatment-resistance in solid cancerous tumors by combining our lead product candidate, TSC, with standard-of-care radiation and chemotherapy regimens, thus effecting a better patient survival outcome without the addition of harmful side effects.

Under normally oxygenated cellular conditions, radiation and chemotherapy generally have a powerful killing effect upon cancerous tumor tissue. However, in many solid tumor types, cellular oxygen deprivation occurs as the result of rapid tumor growth, causing parts of the tumor to outgrow its blood supply. When tumor tissue becomes hypoxic, it is up to three times more resistant to the cancer-killing power of the standard therapies (radiation and chemotherapy) currently used in the treatment of most cancer patients. Cancerous tumor cells are known to thrive under hypoxic conditions, as the resultant changes in the tumor microenvironment confer “treatment-resistance” to radiation and chemotherapy within the cell.

Many solid cancerous tumor types are hypoxic and therefore subject to this treatment-resistance. TSC safely re-oxygenates treatment-resistant hypoxic tumor tissue via a novel mechanism of action, without affecting the oxygenation of normal tissue, thereby increasing therapeutic effectiveness. To date, no addition of serious harmful side effects, or exacerbation of the known side effects of standard-of-care treatments, has been observed in our clinical studies.

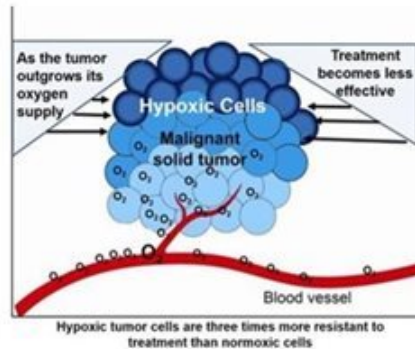
TSC’s distinctive re-oxygenation capabilities derive from its mechanism of action, which promotes enhanced diffusion of oxygen through blood plasma and into the hypoxic tumor microenvironment. Disruption of the treatment-resistance syndrome by re-oxygenation promotes enhanced cancer-killing power from radiation and chemotherapy, thereby safely impacting patient survival. Because of the characteristics of this novel mechanism, oxygen levels of normal tissue remain unaffected, thereby avoiding side effects related to the syndrome referred to as “oxygen toxicity.” We believe this avoidance of oxygen toxicity confers a significant advantage to TSC’s diffusion-based approach over previous attempts to diminish treatment-resistance based on enhancing the oxygen concentration levels of the blood.

Our clinical development plan targets TSC at radiation and chemotherapy sensitization of hypoxic tumor types, with an initial focus on primary brain cancer. We have been granted orphan drug designations by the FDA for the treatment of brain cancers based on the acknowledged unmet medical need and number of patients affected. Such orphan drug designations allow certain favorable treatments under FDA regulations in connection with exclusivity periods and the new drug approval process.

Tumor Hypoxia

We believe that our breakthrough small molecule approach to overcoming solid tumor treatment-resistance by the reduction of cellular hypoxia may have significant implications for the improved treatment of cancer. Hypoxia is a deficiency in the supply of oxygen. It is well known that tumors are especially susceptible to developing hypoxia, driven by a combination of rapid cellular growth, structural abnormalities of the tumor microvessels and disturbed circulation within the tumor. There are a number of known treatment-resistance consequences conferred by tumor hypoxia, including increases in:

- Resistance to ionizing radiation;
- Clinically aggressive phenotype;
- Potential for more invasive growth; and,
- Regional and distal tumor spreading.



The above-described phenomenon of hypoxia-related “treatment-resistance” has been known to the scientific and clinical communities for over half a century. The challenge has been to find an approach that can effectively mitigate treatment-resistance without the addition of toxic side effects or exacerbation of the side effects associated with radiation and chemotherapy treatments. We believe that TSC embodies such an approach.

Stroke and Hypoxia

Nearly 800,000 people in the U.S. suffer from a stroke each year - every 4 minutes, someone loses his/her life as a result of stroke. Stroke is the 5th leading cause of death in the U.S. and the No. 1 cause of adult disability. In the eight major pharmaceutical markets (U.S., France, Germany, Italy, Spain the UK, Japan and China), stroke incidence is approximately 3.4 million people annually.

A stroke is caused by restricted blood flow to the brain, either from a clot (which is called an ischemic stroke, representing about 87% of all strokes) or a burst blood vessel (a hemorrhagic stroke, representing about 13% of strokes). The resulting hypoxia drives the death of millions of neurons per minute, leading to physical impairment and, too often, death for the stroke victim. These two very different causes - clot or bleed - produce almost identical symptoms and there are few treatment options. Treatment is especially complicated by difficulties in determining the difference between ischemic and hemorrhagic stroke, which can only be done by sophisticated imaging equipment in major hospital settings. For those who survive their stroke, the damage is often long-term and significant, with an impact that can be felt among their families and communities.

TSC is believed to enhance the diffusion of oxygen in hypoxic tissues by altering the structure of water molecules in blood plasma, thus facilitating the transport of oxygen to the tissue affected by the stroke, helping prevent neuronal death and related brain damage. Importantly, to date, TSC has shown safety and potential efficacy in both ischemic and hemorrhagic stroke, meaning that it could be administered, prior to a diagnostic MRI, while the patient is still in the ambulance, saving hours.

Trans Sodium Crocetin

Dr. John Gainer, our Chief Scientific Officer, one of our directors and a Professor Emeritus of Chemical Engineering at the University of Virginia, was the first to propose the use of chemical compounds specifically to facilitate the diffusion of oxygen through blood plasma for the purpose of re-oxygenating hypoxic tissues. Dr. Gainer's early laboratory work systematically examined various means to alter the diffusivity of oxygen through the use of small molecules that would affect the intermolecular forces existing in blood plasma. He originally identified crocetin, a natural carotenoid compound, as a molecule that could increase oxygen diffusion through the plasma, and crocetin was shown to be an effective treatment in a rabbit model of atherosclerosis and other indications. This work continued from the 1970s into the mid-1990s with various animal models, including radiation sensitization and hemorrhagic shock.

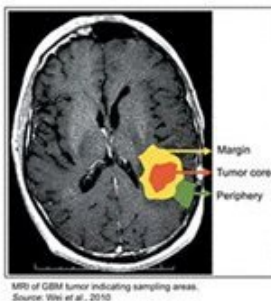
Because crocetin is an isomeric mixture, Dr. Gainer examined whether it was the trans-isomer which was responsible for eliciting the therapeutic benefit. These experiments led to his development of a pure trans-isomer salt compound, which he named trans sodium crocetin. (The USAN designated name is transcrocetin sodium). TSC has been shown to be more effective than crocetin in a severe model of hemorrhagic shock in both rats and pigs. It also demonstrated safety and efficacy in animal models of stroke and myocardial infarction, as well as in enhancing the response of hypoxic tumors to the therapeutic effects of radiation and chemotherapy.

It is proposed that TSC works by altering the molecular arrangement of the water molecules in blood plasma (which is composed of 90% water), with the altered structure being less dense - and thus less resistant to oxygen diffusion - than untreated blood plasma. A water molecule is composed of two hydrogen atoms and one oxygen atom, with a net positive charge found on the hydrogen atoms and a net negative charge found on the oxygen atom. This results in the formation of hydrogen bonds, which are an attraction between the net-negatively charged oxygen of one water molecule and the net-positively charged hydrogen atoms of another water molecule. Theoretically, one water molecule can form four hydrogen bonds with neighboring water molecules. However, the literature on the subject indicates that a water molecule actually forms, on average, 2 to 3.6 hydrogen bonds. By promoting an increase in the average number of hydrogen bonds among the water molecules comprising the bulk of blood plasma, TSC enhances the ability of oxygen to diffuse more easily through the plasma and into hypoxic tissue.

In March 2017, we received a patent relating to bipolar trans carotenoid salts and their uses. This patent expands the coverage of the therapeutic use of TSC and other related compounds to five hypoxia-related conditions including congestive heart failure, chronic renal failure, acute lung injury (ALI), chronic obstructive pulmonary disease (COPD) and respiratory distress syndrome (RDS). In December 2018, we were awarded a patent for the use of TSC in conjunction with Tissue Plasminogen Activator (tPA) for the treatment of stroke. Currently, tPA - a thrombolytic used to break down blood clots in patients suffering from ischemic stroke - is the only FDA-approved therapeutic stroke treatment.

Trans Sodium Crocetinate Increases Oxygenation of Hypoxic Cancerous Tumors

While earlier TSC studies focused on improved treatments for hemorrhagic shock, ischemia, and traumatic brain injury, the use of TSC as an agent to re-oxygenate hypoxic cancerous tumors became a central area of research for us following our founding in 2001. Because tumor hypoxia is a leading cause of solid tumor resistance to both radiation and chemotherapy, it was believed that an agent such as TSC – one that could safely increase the oxygenation of hypoxic tumor tissue – could prove effective in treatment-resistant cancers when combined with standard-of-care regimens of radiation and/or chemotherapy. This belief led to the development of preclinical and clinical development programs targeted against treatment-resistance in various cancers, with a focus on brain cancer, all of which are known to be significantly hypoxic. The Company’s longer term goal is to use TSC against treatment-resistance in the entire range of hypoxic cancers now treated with radiation and chemotherapy.



Glioblastoma Program

Our lead program is targeted against newly diagnosed primary brain cancer, also known as glioblastoma (GBM). Glioblastoma is a grade IV brain tumor, characterized by a heterogeneous cell population, with a number of negative attributes. GBM cells are typically genetically unstable (and thus prone to mutation), highly infiltrative, angiogenic, and resistant to radiation and chemotherapy. The mutations typically found in GBM allow the tumor to grow and thrive in a hypoxic environment. GBM is classified into two major subclasses, primary or secondary, depending upon the clinical properties as well as the chromosomal and genetic alterations that are unique to each class. Primary GBM arises *de novo* from normal glial cells and typically occurs in those over the age of 40, while secondary GBM arises from transformation of lower grade tumors and is usually seen in younger patients. Primary GBM is believed to account for approximately 95% of all GBM diagnoses.

While GBM is the most common form of primary brain tumor involving glial cells, it is still relatively rare, as approximately 12,000 people in the United States were diagnosed with GBM in 2017. The median age of GBM diagnosis is approximately 65 years, with the incidence of GBM in those over 65 increasing rapidly as shown by a doubling in incidence from 5.1 per 100,000 in the 1970s to 10.6 per 100,000 in the 1990s. Those diagnosed with the disease have a grim prognosis, with the median survival time of untreated patients being 4.5 months. Current standard-of-care treatment only provides an average of 14-16 months of survival time after diagnosis.

Current Treatments for GBM

The standard-of-care for GBM tumors generally begins with surgical resection, unless the tumor is deemed inoperable due to its location near vital centers of the brain. This surgery is performed both to alleviate the symptoms associated with the disease as well as to facilitate treatment of residual tumor cells. Even with advances in surgical technique, complete removal of the tumor with clean margins is difficult to achieve, as the tumors are highly infiltrative and typically extend into the normal brain parenchyma. Due to this, almost all GBM patients have recurrence of the tumor, with 90% of such recurrence occurring at the primary site.

Due to the invasive nature of the tumors, surgical resection is usually promptly followed by radiotherapy coupled with the use of chemotherapeutic agents. Radiotherapy involves the administration of irradiation to the brain. While nitrosoureas were historically a commonly used chemotherapeutic agent, temozolomide (“TMZ”) was approved in 2005 and is now a mainstay of the standard-of-care. This is based on a clinical trial that showed the addition of TMZ to surgery and radiation increased median survival in newly diagnosed GBM patients to 14.6 months compared to 12.1 months for the surgery and radiation only group.

Most chemotherapeutic drugs have a limited ability to cross the blood brain barrier, thus a strategy to attempt to circumvent this was the development of Gliadel®, dissolvable chemotherapy wafers that could be placed in the tumor bed following surgical resection. Gliadel® contains the nitrosourea chemotherapeutic agent carmustine that is released for several weeks, in contrast to systemically administered carmustine that has a very short half-life. While Gliadel® wafers were shown to be safe, the drugs’ addition to radiation and TMZ did not result in a statistically significant increase in survival.

GBM tumors show increased expression of vascular endothelial growth factor (“VEGF”), and the anti-angiogenesis drug bevacizumab has been approved by the FDA for the treatment of recurrent GBM. A Phase 2 study found that bevacizumab treatment in patients with recurrent GBM increased six-month progression-free survival from a historical 9-15% to 25% with overall six-month survival of 54%. Another Phase 2 study showed that recurrent GBM patients treated with bevacizumab at a lower dose but a higher frequency had even higher six-month progression-free survival of 42.6%.

While bevacizumab has shown success in recurrent GBM, it is not utilized in newly diagnosed patients, our target patient population, as two separate clinical trials showed no difference in overall survival in patients treated with radiation, TMZ, and bevacizumab compared to patients treated with only radiation and TMZ. Bevacizumab treatment did result in an increase in progression free survival in both studies; however, the reason why this increase in progression free survival did not translate to an increase in overall survival is unclear. In addition, certain studies have reported that patients treated with bevacizumab had an increased symptom burden, a worse quality of life, and a decline in neurocognitive function.

GBM Therapies Under Development

There are a number of companies developing GBM therapies and a search on the website www.clinicaltrials.gov will yield over 300 results for “glioblastoma multiforme” and “open trials.” Most of these trials focus on the recurrent patient population, whereas our target population is newly diagnosed inoperable patients. In addition to the therapeutics previously mentioned, other GBM trials have included Northwest Therapeutics’ DCVax®-L, Bristol-Myers Squibb’s Nivolumab/Ipilimumab and AbbVie’s Veliparib. In addition, the medical device company Novocure has been developing a novel approach called Tumor Treating Fields (“TTFIELDS”) using low intensity, alternating electric fields within the intermediate frequency range. TTFIELDS are believed to disrupt cell division through physical interactions with key molecules during mitosis. This medical device approach has shown some success in both newly diagnosed and recurrent GBM patients and in some geographic areas may be becoming a part of the standard of care. Other recent approaches include combination immuno-oncology trials. For example, Inovio Pharmaceuticals, Inc. has a Phase 1b/2a immuno-oncology safety study underway in patients with newly diagnosed GBM designed to evaluate cemiplimab (also known as REGN2810), a PD-1 inhibitor developed by Regeneron Pharmaceuticals, Inc.), in combination with Inovio’s INO-5401 T cell activating immunotherapy encoding multiple antigens and INO-9012, an immune activator encoding IL-12. The primary endpoints are safety and tolerability but the study will also evaluate immunological impact, progression-free survival and overall survival.

GBM is an Orphan Disease

GBM is diagnosed in approximately 12,000 individuals every year, making it an “orphan disease.” The Orphan Drug Act of 1983 was designed to provide financial incentives for, and to reduce the costs associated with, developing drugs for rare diseases and disorders. A “rare disease or disorder” is defined by the Orphan Drug Act of 1983 as affecting fewer than 200,000 Americans at the time of designation or one for which “there is no reasonable expectation that the cost of developing and making available in the United States...will be recovered from sales in the United States.” A sponsor must request that the FDA designate a drug currently under development for a “rare disease or condition” as an orphan drug, and if the FDA agrees that the drug and indication meet the criteria set forth in the Orphan Drug Act of 1983, certain financial and marketing incentives become available.

In July 2011, we announced that TSC was granted Orphan Drug Designation by the FDA for the treatment of GBM. RES-529 was also granted Orphan Drug Designation in January 2015.

Trans Sodium Crocetinate Phase 1/2 Clinical Trial in GBM

We have evaluated TSC in 128 human subjects in various Phase 1 and Phase 2 clinical trials to date, with no serious adverse events attributable to TSC.

Our Phase 1/2 clinical trial in GBM enrolled 59 newly diagnosed patients who received TSC in conjunction with radiation and TMZ. In the Phase 1 portion of the trial, TSC was initially administered three times per week at half-dose to three patients prior to radiation. Subsequently, six additional patients received full-dose TSC for six weeks in combination with radiation. No dose-limiting toxicities were identified in the nine patients during the Phase 1 portion of the trial, nor were any serious adverse events relating to the drug observed. Fifty additional patients were enrolled in the Phase 2 trial and received full-dose TSC in combination with TMZ and radiation therapy. Four weeks after completion of radiation therapy, all patients underwent chemotherapy with higher doses of TMZ for five (5) days every four weeks, but no further TSC was administered.

We presented initial results from the trial at the 2015 American Society of Clinical Oncology (“ASCO”) Annual Meeting in June 2015, which discussed data from the 18 trial sites covering the first twenty-one months. Final results were published in the Journal of Neurosurgery online in May 2016. We compared results in relation to a historical control group from a 2005 study which showed that the addition of TMZ to standard-of-care (surgery plus radiation) increased overall survival from 12.1 months to 14.6 months. We reported that:

- TSC plus radiation and TMZ increased the patients’ chance of survival at two years by 37% compared to the historical control group. The overall survival at two years was 36.3% in the TSC group compared to 26.5% in the historical control group.
- In the subgroup of patients considered inoperable, the chance of survival at two years for those who received TSC was increased by 380%, (40% alive at two years for TSC group versus 10% for control).
- 71% of those treated with TSC were alive at one year compared to 61% of those in the historical control group. In 11 of 56 patients, tumors regressed to undetectable.
- No serious safety findings attributed to TSC were observed in the TSC study and adverse events were consistent with those seen in previous trials of GBM featuring radiation and TMZ.

End-of-Phase 2 FDA Meeting and TSC Phase 3 GBM Clinical Trial

Following the announcement of the results of the 2015 Phase 1/2 clinical trial in GBM, we held an end of Phase 2 meeting with the FDA in August 2015 to discuss planning for a Phase 3 clinical trial. At the meeting and subsequent thereto, guidance was received on a trial design for the Phase 3 study, including:

- A single, randomized trial of the agreed upon design, if successful, can serve as the basis for an application for approval.

- The trial will consist of 236 newly diagnosed inoperable GBM patients with half given TSC in conjunction with standard-of-care radiation and TMZ and half receiving standard-of-care radiation and TMZ only.
- Based on the Phase 1/2 safety results with supporting toxicology, TSC's dosing exposure will be substantially increased, which means that TSC can now be used for both the radiation + chemotherapy and subsequent TMZ chemotherapy-only phase of GBM treatment, extending the TSC treatment duration from 6 weeks to 30 weeks.
- Diffusion will provide certain expanded information on animal toxicology, pharmacokinetics and manufacturing practices to the FDA before initiating the trial.

Phase 3 INTACT clinical trial is currently enrolling

The INTACT clinical trial is an open-label, randomized, controlled, Phase 3 safety and efficacy registration trial. Subjects will be randomized at baseline to standard of care ("SOC") for first-line treatment of GBM plus TSC, or to SOC alone. The SOC for GBM is TMZ plus radiation therapy ("RT") for 6 weeks followed by 28 days of rest, followed by 6 cycles of post-radiation TMZ treatment.

TSC is being administered during both the RT and post-radiation TMZ treatment periods.

During the RT treatment period subjects receive:

- Focal RT delivered as 60Gy/30 fractions scheduled at 2Gy/day for 5 days each week (Monday through Friday) for 6 weeks.
- Temozolomide 75 mg/m² orally once daily (usually administered the night preceding each RT session) starting the evening before the first RT session over a period of 42 calendar days with a maximum of 49 days.
- TSC 0.25 mg/kg IV for 3 days each week (e.g., Monday, Wednesday, Friday or other schedule that supplies a minimum 3 TSC doses per week) administered between 45 to 60 minutes prior to each RT session.

During the 28-day rest period all subjects receive no treatment.

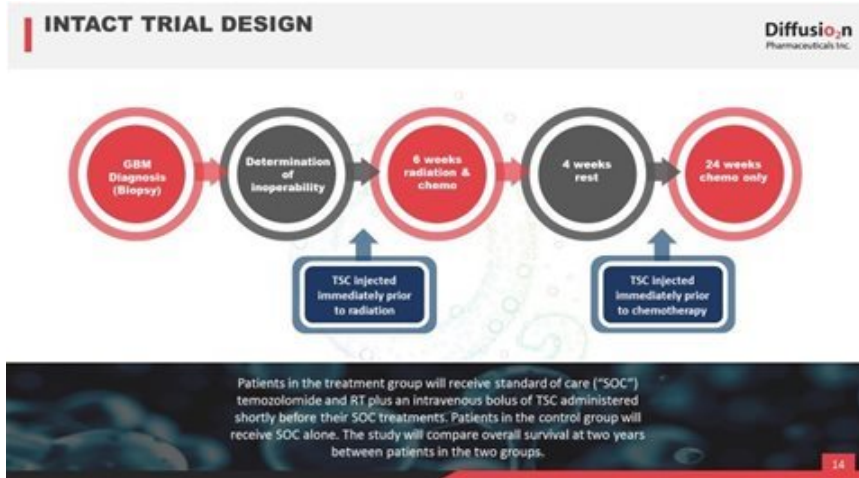
During the post-radiation 6-cycle temozolomide treatment period:

- All subjects will receive 28-day oral temozolomide (150 mg/m² first cycle and 200 mg/m² all subsequent cycles as tolerated) administered on Day 1-5 (Monday through Friday) of each 28-day cycle.
- Controls will receive oral temozolomide at night at home per the SOC and are not required to attend clinic visits during this period.
- Subjects randomized to TSC will receive TSC 1.5 mg/kg (or another dose if recommended by the DSMB) 1.5 to 2 hours before their temozolomide dose during the daytime for 3 days during the first week of each 28-day cycle (Days 1, 3, 5; e.g., Monday, Wednesday, Friday or other schedule that supplies at minimum 3 TSC doses per week). The Tuesday, Thursday doses will be given at night at home. Long-acting antiemetics may be administered prior to daytime temozolomide dosing on Days 1, 3, 5.

The safety, tolerability and pharmacokinetics ("PK") of TSC at higher doses than 0.25 mg/kg with temozolomide is being assessed during adjuvant therapy. TSC at doses between 0.25 mg/kg and up to 1.5 mg/kg in combination with concomitant temozolomide is being assigned (not randomized) in the first 8 subjects enrolled in the INTACT trial. These patients undergo RT plus temozolomide plus TSC treatment (0.25 mg/kg) for 6 weekly cycles followed by 4 weeks of rest in standard fashion. At the Week 10 clinic visit the same 8 subjects will be assigned to treatment, with 2 subjects each assigned to TSC at doses of 0.25, 0.50, 1.0 and 1.5 mg/kg. These subjects will be studied in parallel for 2 full 28-day cycles with inclusion of appropriate blood sampling collection for TSC and temozolomide PK. The Data Safety Monitoring Board ("DSMB") will examine the resultant safety data after 2 full cycles (Weeks 11 through 18 of post-radiation temozolomide treatment period; Days 1 to 56). The DSMB may recommend continued use of the 1.5 mg/kg TSC dose for the post-radiation temozolomide treatment period, or may prescribe another dose based on their observations. Subjects then entering into the INTACT trial will be randomized at baseline between TSC plus SOC, or SOC alone.

The baseline assessment for determining progression-free survival (“PFS”) and overall response rate (“ORR”) will be at 10 weeks via MRI using the “modified Response Assessment in Neuro-Oncology” (“mRANO”), and to rule out pseudo-progression. The hazard ratio for the trial will be 0.67, which corresponds to 22% two-year survival in the TSC arm, the lower limit of the 95% confidence interval for the biopsy-only subjects in our Phase 2 trial of TSC for GBM, and 10% survival in the SOC arm. The estimated median survival is therefore 10 months for the SOC arm vs. 14.9 months for the TSC plus SOC arm. In order to achieve 80% power, the trial requires 118 subjects in each arm.

The study will achieve the designed 80% statistical power at 198 events, where an event is defined as death. The first analysis will occur at the earlier of two years follow-up for all subjects or 198 events.



As noted above, the Company will need to raise additional capital in order to complete the Phase 3 INTACT clinical trial, and there is no guarantee the Company will be able to raise the necessary capital. See “Item 1A. Risk Factors” below for additional detail on risks related to the Company’s financing needs and its business generally.

TSC in Pancreatic Cancer and Brain Metastases

Other cancerous tumor targets upon which the Company’s technology is focused include pancreatic cancer and brain metastasis, for which an FDA Orphan Designation has been granted to TSC. We believe that TSC programs for such cancers are Phase 2 ready, as safety profiles have been demonstrated in other oncology programs, protocols have been written, FDA interaction has taken place, and key opinion leaders have been engaged. Further research and development of TSC as a potential treatment for these indications is largely dependent on the necessary financial resources becoming available.

Plans for TSC Phase 2 Clinical Trial for Treatment of Acute Stroke

In addition to the Phase 3 trial for TSC as a potential treatment of GBM, we anticipate beginning enrollment for our Phase 2 Pre Hospital Acute Stroke Therapy - TSC (PHAST - TSC) trial for TSC as a treatment of acute stroke during 2019. We believe that TSC is a promising neurotherapeutic that enhances the diffusion of oxygen in hypoxic tissues by altering the structure of water molecules in blood plasma, thus facilitating the transport of oxygen to the site of the stroke and helping prevent brain tissue damage and neuronal death. TSC has shown benefit for both ischemic and hemorrhagic stroke in preclinical studies.

The planned Phase 2, randomized, double-blind, placebo-controlled trial calls for administering TSC to ambulance-transported patients within two hours of the onset of a suspected acute stroke. It is anticipated that 160 patients will be enrolled in this trial. The pre-hospital, ambulance-based treatment strategy will be conducted in cooperation with the University of California-Los Angeles and the University of Virginia.

Products

We have rights to and own technologies and potential products beyond those described above, including analog molecules as backups to TSC. It is our strategy to focus at the current time on TSC for oncology, specifically GBM, as well as acute stroke. At the current time, the bulk of our cash resources for clinical development is dedicated to the Phase 3 trial for TSC in inoperable GBM and starting the Phase 2 trial for TSC in stroke. We believe we have adequate cash resources to continue operations into July 2019, and we will need to raise additional funds in order to complete these trials. Beyond those described herein, we also intend to continue to review our technologies and potential products on a regular basis and consider internal development in the future and the potential to out-license portions of our technology and potential products to other biopharmaceutical companies with greater focus and resources than ours, or potentially in-license late stage products which are in or ready for human clinical trials.

Also, we own product candidates for ophthalmology, oncology and dermatology. One such product candidate is RES-529, a novel PI3K/Akt/mTOR pathway inhibitor which has completed two Phase I clinical trials for age-related macular degeneration and is in preclinical development in oncology, specifically GBM. The novel inhibition of the PI3K/Akt/mTOR pathway and targeting of the androgen receptor have also shown potential in a number of additional indications. As mentioned previously, RES-529 was granted Orphan Drug Designation in January 2015 for the treatment of GBM.

We are exploring partnering opportunities for our product candidates, such as strategic partnerships, alliances or licensing arrangements. These strategic partnerships could take the form of a merger, a license of our product candidates or an outright sale of our product candidates. In connection with a strategic partnership, we may have to relinquish valuable rights to our product candidates, which could materially decrease any potential returns on our investment in our product candidates, or grant licenses on terms that are not favorable to us or are less favorable than we would have received upon completion of our product research and testing.

Competition

Our industry is highly competitive and subject to rapid and significant change. Potential competitors in the United States are numerous and include major pharmaceutical and specialty pharmaceutical companies, universities and other institutions. We generally divide our competition in the pharmaceutical industry into four categories: (1) companies with large research and developmental departments that develop and market products in many therapeutic areas; (2) companies that have moderate research and development capabilities and focus their product strategy on a small number of therapeutic areas; (3) small companies with limited development capabilities and only a few product offerings; and (4) university and other research institutions. Many of our competitors have longer operating histories, greater name recognition, substantially greater financial resources and larger research and development staffs than we do, as well as substantially greater experience than us in developing products, obtaining regulatory approvals, and manufacturing and marketing pharmaceutical products. A significant amount of research is carried out at academic and government institutions. These institutions are aware of the commercial value of their findings and are aggressive in pursuing patent protection and negotiating licensing arrangements to collect royalties for use of technology that they have developed.

There are several firms, including NuvOx and Hemoglobin Oxygen Therapeutics LLC, currently developing or marketing products that may be competitive with our products, including therapeutics and devices. We believe TSC is a first-in-class novel small molecule that re-oxygenates hypoxic tissue, enhancing efficacy of radiation and chemotherapy without harmful side effects.

Mergers and acquisitions in the pharmaceutical and biotechnology industries may result in even more resources being concentrated among a smaller number of our competitors. Our commercial opportunity could be reduced or eliminated if our competitors develop or market products or other novel therapies that are more effective, safer or less costly than our current or future product candidates, or obtain regulatory approval for their products more rapidly than we may obtain approval for our product candidates. In addition, the first product to reach the market in a therapeutic or preventative area is often at a significant competitive advantage relative to later entrants in the market and may result in certain marketing exclusivity as per federal legislation. Acceptance by physicians and other health care providers, including managed care groups, also is critical to the success of a product versus competitor products. Our success will be based in part on our ability to identify, develop and manage a portfolio of product candidates that are safer and more effective than competing products.

Research and Product Development

We incurred approximately \$5.8 million in 2018 and \$5.1 million in 2017 on research and product development activities that related primarily to activities associated with the synthesis and formulations of our products then in development, additional preclinical studies and planning for Phase I/Phase II studies. We anticipate that our research and development expenses during 2019 will increase compared to 2018 and will consist primarily of expenses associated with the initiation of our glioblastoma and stroke TSC clinical trials.

Intellectual Property

Our success depends and will continue to depend in part upon our ability to maintain proprietary protection for our products and technologies, to preserve our proprietary information, trademarks and trade secrets and to operate without infringing the proprietary rights of others. Our policy is to attempt to protect our technology by, among other things, filing patent applications on inventions that are important to the development and conduct of our business with the U.S. Patent and Trademark Office (“USPTO”), and its foreign counterparts or obtaining license rights for technology that we consider important to the development of our business.

As of December 31, 2018, we owned approximately 16 issued U.S. patents and 40 issued foreign patents, which include granted European, Japanese, Chinese and Indian patent rights, and over 30 pending patent applications worldwide, covering the product candidates we currently intend to develop. Our current patents expire between 2023 and 2031. TSC has been granted Orphan Drug Designation for the treatment of both GBM and metastatic brain cancer. A formulation patent provides protection for the TSC oral drug product until 2031 with extensions possible.

Patents extend for varying periods according to the date of patent filing or grant and the legal term of patents in various countries where patent protection is obtained. The actual protection afforded by a patent, which can vary from country to country, depends on the type of patent, the scope of its coverage and the availability of legal remedies in the country.

In addition to patents, we use other forms of protection, such as trademark, copyright and trade secret protection, to protect our intellectual property, particularly where we do not believe patent protection is appropriate or obtainable. We aim to take advantage of all of the intellectual property rights that are available to us and believe that this comprehensive approach will provide us with proprietary positions for our product candidates, where available.

We also protect our proprietary information by requiring our employees, consultants, contractors and other advisors to execute nondisclosure and assignment of invention agreements upon commencement of their respective employment or engagement. Agreements with our employees also prevent them from bringing the proprietary rights of third parties to us. In addition, we also require confidentiality or service agreements from third parties that receive our confidential information or materials.

Manufacturing and Supply

We do not have any facilities suitable for manufacturing on a commercial scale any of our product candidates nor do we have any experience in volume manufacturing. We currently use third-party cGMP contract manufacturing organizations (“CMOs”) to manufacture our product candidates for our preclinical studies and clinical trials and intend to continue doing so in the future in accordance with FDA and other appropriate regulations. We anticipate that these CMOs will have capacity to support commercial scale, but we do not have any formal agreements at this time with any of these CMOs to cover commercial production. We also may elect to pursue other CMOs for manufacturing supplies for later-stage trials and for commercialization. We currently have no plans to establish a manufacturing capability, but rather plan to continue to rely on third-party cGMP manufacturers for any future trials and commercialization of our product candidates for which we retain manufacturing responsibility.

Sales and Marketing

We currently have no sales and marketing personnel to sell any of our product candidates on a commercial basis if and when our product candidates received required regulatory approvals. If and when we are ready to commercially launch a product, we will either contract with or hire qualified sales and marketing personnel or seek a joint marketing partner or licensee to assist us with this function.

Government Regulation

FDA Drug Approval Process

In the United States, pharmaceutical products are subject to extensive regulation by the FDA. The Federal Food, Drug, and Cosmetic Act (the “FDC Act”) and other federal and state statutes and regulations, govern, among other things, the research, development, testing, manufacture, storage, recordkeeping, approval, labeling, promotion and marketing, distribution, post-approval monitoring and reporting, sampling and import and export of pharmaceutical products. Failure to comply with applicable U.S. requirements may subject a company to a variety of administrative or judicial sanctions, such as FDA refusal to approve pending new drug applications (“NDAs”), warning or untitled letters, product recalls, product seizures, total or partial suspension of production or distribution, injunctions, fines, civil penalties and criminal prosecution.

Pharmaceutical product development for a new product or certain changes to an approved product in the United States typically involves preclinical laboratory and animal tests, the submission to the FDA of an investigational new drug application (“IND”) which must become effective before clinical testing may commence, and adequate and well-controlled clinical trials to establish the safety and effectiveness of the drug for each indication for which FDA approval is sought. Satisfaction of FDA pre-market approval requirements typically takes many years and the actual time required may vary substantially based upon the type, complexity and novelty of the product or disease.

Preclinical tests include laboratory evaluation of product chemistry, formulation and toxicity, as well as animal trials to assess the characteristics and potential safety and efficacy of the product. The conduct of the preclinical tests must comply with federal regulations and requirements, including good laboratory practices. The results of preclinical testing are submitted to the FDA as part of an IND, along with other information, including information about product chemistry, manufacturing and controls and a proposed clinical trial protocol. Long term preclinical tests, such as animal tests of reproductive toxicity and carcinogenicity, may continue after the IND is submitted.

A 30-day waiting period after the submission of each IND is required prior to the commencement of clinical testing in humans. If the FDA has neither commented on nor questioned the IND within this 30-day period, the clinical trial proposed in the IND may begin.

Clinical trials involve the administration of the investigational new drug to healthy volunteers or patients under the supervision of a qualified investigator. Clinical trials must be conducted: (1) in compliance with federal regulations; (2) in compliance with good clinical practice (“GCP”) an international standard meant to protect the rights and health of patients and to define the roles of clinical trial sponsors, administrators and monitors; and (3) under protocols detailing the objectives of the trial, the parameters to be used in monitoring safety and the effectiveness criteria to be evaluated. Each protocol involving testing on U.S. patients and subsequent protocol amendments must be submitted to the FDA as part of the IND.

The FDA may order the temporary or permanent discontinuation of a clinical trial at any time, or impose other sanctions, if it believes that the clinical trial either is not being conducted in accordance with FDA requirements or presents an unacceptable risk to the clinical trial patients. The study protocol and informed consent information for patients in clinical trials must also be submitted to an institutional review board (“IRB”) for approval at each site at which the clinical trial will be conducted. An IRB may also require the clinical trial at the site to be halted, either temporarily or permanently, for failure to comply with the IRB’s requirements, or may impose other conditions.

Clinical trials to support NDAs for marketing approval are typically conducted in three sequential phases, but the phases may overlap, especially in cancer indications. In Phase 1, the initial introduction of the drug into healthy human subjects or patients, the drug is tested to assess pharmacological actions, side effects associated with increasing doses and, if possible, early evidence on effectiveness. Phase 2 usually involves trials in a limited patient population to determine metabolism, pharmacokinetics, the effectiveness of the drug for a particular indication, dosage tolerance and optimum dosage, and to identify common adverse effects and safety risks. If a compound demonstrates evidence of effectiveness and an acceptable safety profile in Phase 2 evaluations, Phase 3 clinical trials are undertaken to obtain the additional information about clinical efficacy and safety in a larger number of patients, typically at geographically dispersed clinical trial sites, to permit the FDA to evaluate the overall benefit-risk relationship of the drug and to provide adequate information for the labeling of the drug. In most cases the FDA requires two adequate and well-controlled Phase 3 clinical trials with statistically significant results to demonstrate the efficacy of the drug. With suitable FDA agreement, a single Phase 3 clinical trial with other confirmatory evidence may be sufficient. In those instances, the study is usually a large multicenter trial demonstrating internal consistency and a statistically persuasive finding of an effect on mortality, irreversible morbidity or prevention of a disease with a potentially serious outcome and confirmation of the result in a second trial would be practically or ethically impossible.

After completion of the required clinical testing, an NDA is prepared and submitted to the FDA. FDA approval of the NDA is required before marketing of the product may begin in the United States. The NDA must include the results of all preclinical, clinical and other testing and a compilation of data relating to the product’s pharmacology, chemistry, manufacture and controls. The cost of preparing and submitting an NDA is substantial. The submission of most NDAs is additionally subject to a substantial application user fee, and the manufacturer and sponsor under an approved new drug application are also subject to annual product and establishment user fees. These fees are typically increased annually.

The FDA has sixty (60) days from its receipt of an NDA to determine whether the application will be accepted for filing based on the agency’s threshold determination that it is sufficiently complete to permit substantive review. Once the submission is accepted for filing, the FDA begins an in-depth review. The FDA has agreed to certain performance goals in the review of new drug applications. Priority review can be applied to drugs that the FDA determines offer major advances in treatment, or provide a treatment where no adequate therapy exists. For certain drugs, priority review is further limited only for drugs intended to treat a serious or life-threatening disease relative to the currently approved products. The review process for both standard and priority review may be extended by the FDA for three (3) additional months to consider certain late-submitted information, or information intended to clarify information already provided in the submission.

The FDA may also refer applications for novel drug products, or drug products that present difficult questions of safety or efficacy, to an advisory committee, typically a panel that includes clinicians and other experts, for review, evaluation and a recommendation as to whether the application should be approved. The FDA is not bound by the recommendation of an advisory committee, but it generally follows such recommendations. Before approving an NDA, the FDA will typically inspect one or more clinical sites to assure compliance with GCP. Additionally, the FDA will inspect the facility or the facilities at which the drug is manufactured. The FDA will not approve the product unless compliance with current good manufacturing practice (“cGMP”) is satisfactory and the NDA contains data that provide substantial evidence that the drug is safe and effective in the indication studied.

After the FDA evaluates the NDA and the manufacturing facilities, it issues either an approval letter or a complete response letter. A complete response letter generally outlines the deficiencies in the submission and may require substantial additional testing, or information, in order for the FDA to reconsider the application. If, or when, those deficiencies have been addressed to the FDA’s satisfaction in a resubmission of the NDA, the FDA will issue an approval letter. The FDA has committed to reviewing such resubmissions in two or six (6) months depending on the type of information included.

An approval letter authorizes commercial marketing of the drug with specific prescribing information for specific indications. As a condition of NDA approval, the FDA may require a risk evaluation and mitigation strategy (“REMS”) to help ensure that the benefits of the drug outweigh the potential risks. REMS can include medication guides, communication plans for healthcare professionals and elements to assure safe use (“ETASU”). ETASU can include, but are not limited to, special training or certification for prescribing or dispensing, dispensing only under certain circumstances, special monitoring and the use of patient registries. The requirement for a REMS can materially affect the potential market and profitability of the drug. Moreover, product approval may require substantial post-approval testing and surveillance to monitor the drug’s safety or efficacy. Once granted, product approvals may be withdrawn if compliance with regulatory standards is not maintained or problems are identified following initial marketing.

Changes to some of the conditions established in an approved application, including changes in indications, labeling, or manufacturing processes or facilities, require submission and FDA approval of a new NDA or NDA supplement before the change can be implemented. An NDA supplement for a new indication typically requires clinical data similar to that in the original application, and the FDA uses the same procedures and actions in reviewing NDA supplements as it does in reviewing NDAs.

The Hatch-Waxman Act

Orange Book Listing

In seeking approval for a drug through an NDA, applicants are required to list with the FDA each patent whose claims cover the applicant’s product. Upon approval of a drug, each of the patents listed in the application for the drug is then published in the FDA’s Approved Drug Products with Therapeutic Equivalence Evaluations, commonly known as the Orange Book. Drugs listed in the Orange Book can, in turn, be cited by potential generic competitors in support of approval of an abbreviated new drug application (“ANDA”). An ANDA provides for marketing of a drug product that has the same active ingredients in the same strengths and dosage form as the listed drug and has been shown through bioequivalence testing to be therapeutically equivalent to the listed drug. Other than the requirement for bioequivalence testing, ANDA applicants are not required to conduct, or submit results of, preclinical or clinical tests to prove the safety or effectiveness of their drug product. Drugs approved in this way are commonly referred to as “generic equivalents” to the listed drug, and can often be substituted by pharmacists under prescriptions written for the original listed drug.

The ANDA applicant is required to certify to the FDA concerning any patents listed for the approved product in the FDA’s Orange Book. Specifically, the applicant must certify that: (1) the required patent information has not been filed; (2) the listed patent has expired; (3) the listed patent has not expired, but will expire on a particular date and approval is sought after patent expiration; or (4) the listed patent is invalid or will not be infringed by the new product. The ANDA applicant may also elect to submit a section viii statement certifying that its proposed ANDA label does not contain (or carves out) any language regarding the patented method-of-use rather than certify to a listed method-of-use patent. If the applicant does not challenge the listed patents, the ANDA will not be approved until all the listed patents claiming the referenced product have expired.

A certification that the new product will not infringe the already approved product’s listed patents, or that such patents are invalid, is called a Paragraph IV certification. If the ANDA applicant has provided a Paragraph IV certification to the FDA, the applicant must also send notice of the Paragraph IV certification to the NDA and patent holders once the ANDA has been accepted for filing by the FDA. The NDA and patent holders may then commence a patent infringement lawsuit in response to the notice of the Paragraph IV certification. The filing of a patent infringement lawsuit within forty-five (45) days of the receipt of a Paragraph IV certification automatically prevents the FDA from approving the ANDA until the earlier of thirty (30) months, expiration of the patent, settlement of the lawsuit, or a decision in the infringement case that is favorable to the ANDA applicant.

The ANDA also will not be approved until any applicable non-patent exclusivity listed in the Orange Book for the referenced product has expired.

Exclusivity

Upon NDA approval of a new chemical entity (“NCE”) which is a drug that contains no active moiety that has been approved by the FDA in any other NDA, that drug receives five years of marketing exclusivity during which the FDA cannot receive any ANDA seeking approval of a generic version of that drug. Certain changes to a drug, such as the addition of a new indication to the package insert, are associated with a three-year period of exclusivity during which the FDA cannot approve an ANDA for a generic drug that includes the change.

An ANDA may be submitted one year before NCE exclusivity expires if a Paragraph IV certification is filed. If there is no listed patent in the Orange Book, there may not be a Paragraph IV certification and, thus, no ANDA may be filed before the expiration of the exclusivity period.

Risk Evaluation and Mitigation Strategies (REMS)

The FDA has the authority to require a REMS to ensure the safe use of the drug. In determining whether a REMS is necessary, the FDA must consider the size of the population likely to use the drug, the seriousness of the disease or condition to be treated, the expected benefit of the drug, the duration of treatment, the seriousness of known or potential adverse events, and whether the drug is a new molecular entity. If the FDA determines a REMS is necessary, the drug sponsor must agree to the REMS plan at the time of approval. A REMS may be required to include various elements, such as a medication guide or patient package insert, a communication plan to educate healthcare providers of the drug’s risks, limitations on who may prescribe or dispense the drug, or other measures that the FDA deems necessary to assure the safe use of the drug. REMS can include medication guides, communication plans for healthcare professionals, and ETASU. ETASU can include, but are not limited to, special training or certification for prescribing or dispensing, dispensing only under certain circumstances, special monitoring, and the use of patient registries. In addition, the REMS must include a timetable to periodically assess the strategy. The FDA may also impose a REMS requirement on a drug already on the market if the FDA determines, based on new safety information, that a REMS is necessary to ensure that the drug’s benefits outweigh its risks. The requirement for a REMS can materially affect the potential market and profitability of a drug.

Patent Term Extension

After NDA approval, owners of relevant drug patents may apply for up to a five-year patent extension. The allowable patent term extension is calculated as half of the drug’s testing phase, the time between IND application and NDA submission, and all of the review phase, the time between NDA submission and approval, up to a maximum of five years. The time can be shortened if the FDA determines that the applicant did not pursue approval with due diligence. The total patent term after the extension may not exceed 14 years.

For patents that might expire during the application phase, the patent owner may request an interim patent extension. An interim patent extension increases the patent term by one year and may be renewed up to four times. For each interim patent extension granted, the post-approval patent extension is reduced by one year. The director of the USPTO must determine that approval of the drug covered by the patent for which a patent extension is being sought is likely. Interim patent extensions are not available for a drug for which an NDA has not been submitted.

Post-Approval Requirements

Once an NDA is approved, a product will be subject to certain post-approval requirements. For instance, the FDA closely regulates the post-approval marketing and promotion of drugs, including standards and regulations for direct-to-consumer advertising, off-label promotion, industry-sponsored scientific and educational activities and promotional activities involving the internet. Drugs may be marketed only for the approved indications and in accordance with the provisions of the approved labeling.

Adverse event reporting and submission of periodic reports is required following FDA approval of an NDA. The FDA also may require post-marketing testing, known as Phase 4 testing, REMS, and surveillance to monitor the effects of an approved product, or the FDA may place conditions on an approval that could restrict the distribution or use of the product. In addition, quality-control, drug manufacture, packaging and labeling procedures must continue to conform to cGMPs after approval. Drug manufacturers and certain of their subcontractors are required to register their establishments with the FDA and certain state agencies. Registration with the FDA subjects entities to periodic unannounced inspections by the FDA, during which the agency inspects manufacturing facilities to assess compliance with cGMPs. Accordingly, manufacturers must continue to expend time, money and effort in the areas of production and quality-control to maintain compliance with cGMPs. Regulatory authorities may withdraw product approvals or request product recalls if a company fails to comply with regulatory standards, if it encounters problems following initial marketing, or if previously unrecognized problems are subsequently discovered.

Pediatric Information

Under the Pediatric Research Equity Act, NDAs or supplements to NDAs must contain data to assess the safety and effectiveness of the drug for the claimed indications in all relevant pediatric subpopulations and to support dosing and administration for each pediatric subpopulation for which the drug is safe and effective. The FDA may grant full or partial waivers, or deferrals, for submission of data.

The Best Pharmaceuticals for Children Act (“BPCA”) provides NDA holders a six-month extension of any exclusivity, patent or non-patent, for a drug if certain conditions are met. Conditions for exclusivity include the FDA’s determination that information relating to the use of a new drug in the pediatric population may produce health benefits in that population, the FDA making a written request for pediatric studies and the applicant agreeing to perform, and reporting on, the requested studies within the statutory timeframe. Applications under the BPCA are treated as priority applications, with all of the benefits that designation confers.

The Orphan Drug Act of 1983

The Orphan Drug Act of 1983 was designed to provide financial incentives for, and to reduce the costs associated with, developing drugs for rare diseases and disorders. A “rare disease or disorder” is defined by the Orphan Drug Act of 1983 as affecting fewer than 200,000 Americans at the time of designation or one for which “there is no reasonable expectation that the cost of developing and making available in the United States...will be recovered from sales in the United States.” A sponsor must request that the FDA designate a drug currently under development for a “rare disease or condition” as an orphan drug, and if the FDA agrees that the drug and indication meet the criteria set forth in the Orphan Drug Act of 1983, certain financial and marketing incentives become available. As mentioned previously, we have received Orphan Drug designations related to TSC and RES-529 for the treatment of GBM and for TSC related to the treatment of metastatic brain cancer.

Disclosure of Clinical Trial Information

Sponsors of clinical trials of FDA-regulated products, including drugs, are required to register and disclose certain clinical trial information. Information related to the product, patient population, phase of investigation, study sites and investigators and other aspects of the clinical trial is then made public as part of the registration. Sponsors are also obligated to discuss the results of their clinical trials after completion. Disclosure of the results of these trials can be delayed until the new product or new indication being studied has been approved. Competitors may use this publicly-available information to gain knowledge regarding the progress of development programs.

Regulation Outside of the United States

In addition to regulations in the United States, we will be subject to regulations of other countries governing any clinical trials and commercial sales and distribution of our product candidates. Whether or not we obtain FDA approval for a product, we must obtain approval by the comparable regulatory authorities of countries outside of the United States before we can commence clinical trials in such countries and approval of the regulators of such countries or economic areas, such as the European Union, before we may market products in those countries or areas. Certain countries outside of the United States have a process similar to the FDA's that requires the submission of a clinical trial application ("CTA") much like the IND prior to the commencement of human clinical trials. In the European Union, for example, a CTA must be submitted to each country's national health authority and an independent ethics committee, much like the FDA and IRB, respectively. Once the CTA is approved in accordance with a country's requirements, clinical trial development may proceed. The approval process and requirements governing the conduct of clinical trials, product licensing, pricing and reimbursement vary greatly from place to place, and the time may be longer or shorter than that required for FDA approval.

Under European Union regulatory systems, a company may submit marketing authorization applications either under a centralized or decentralized procedure. The centralized procedure, which is compulsory for medicines produced by biotechnology or those medicines intended to treat AIDS, cancer, neurodegenerative disorders or diabetes and is optional for those medicines which are highly innovative, provides for the grant of a single marketing authorization that is valid for all European Union member states. The decentralized procedure provides for mutual recognition of national approval decisions. Under this procedure, the holder of a national marketing authorization may submit an application to the remaining member states. Within ninety (90) days of receiving the applications and assessments report, each member state must decide whether to recognize approval. If a member state does not recognize the marketing authorization, the disputed points are eventually referred to the European Commission, whose decision is binding on all member states.

Anti-Kickback and False Claims 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 pharmaceutical industry. These laws include, among others, anti-kickback statutes, false claims statutes and other statutes pertaining to healthcare fraud and abuse. The federal healthcare 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 healthcare item or service reimbursable under Medicare, Medicaid or other federally financed healthcare programs. The Patient Protection and Affordable Care Act, as amended by the Health Care and Education Affordability Reconciliation Act of 2010, collectively referred to as the Affordable Care Act amended the intent element of the federal anti-kickback statute so that a person or entity no longer needs to have actual knowledge of the statute or specific intent to violate it. This statute has been interpreted to apply to arrangements between pharmaceutical manufacturers on the 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 or other regulatory sanctions, 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 qualify for an exception or safe harbor.

Federal false claims laws prohibit any person or entity from, among other things, 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 have a false claim paid. This includes claims made to programs where the federal government reimburses, such as Medicaid, as well as programs where the federal government is a direct purchaser, such as when it purchases off the Federal Supply Schedule. Pharmaceutical and other healthcare companies have been prosecuted under these laws for, among other things, allegedly inflating drug prices they report to pricing services, which in turn were used by the government to set Medicare and Medicaid reimbursement rates, and for allegedly providing free product to customers with the expectation that the customers would bill federal programs for the product. In addition, certain marketing practices, including off-label promotion, may also violate federal false claims laws. Additionally, Affordable Care Act amended the federal healthcare program anti-kickback statute such that a violation of that statute can serve as a basis for liability under certain federal false claims laws.

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.

Other federal statutes pertaining to healthcare fraud and abuse include the civil monetary penalties statute, which prohibits, among other things, the offer or payment of remuneration to a Medicaid or Medicare beneficiary that the offeror or payor knows or should know is likely to influence the beneficiary to order or receive a reimbursable item or service from a particular supplier, and the healthcare fraud and false statements statutes, which prohibit, among other things, knowingly and willfully executing or attempting to execute a scheme to defraud any healthcare benefit program or obtain by means of false or fraudulent pretenses, representations, or promises any money or property owned by or under the control of any healthcare benefit program in connection with the delivery of or payment for healthcare benefits, items, or services.

Violations of these federal healthcare fraud and abuse laws are punishable by imprisonment, criminal fines, civil monetary penalties and exclusion from participation in federal healthcare programs.

It is uncertain whether there will be any legislation that will replace or amend the Affordable Care Act. In addition, the Trump Administration has and will appoint many new secretaries, directors and the like into positions of authority in the U.S. Federal government dealing with the pharmaceutical and healthcare industries that may potentially have a negative impact on the prices and regulatory pathways for certain pharmaceuticals and healthcare products developed by the Company to market and sell its products in the U.S.

Other Federal and State Regulatory Requirements

The Centers for Medicare & Medicaid Services (“CMS”) has issued a final rule pursuant to Affordable Care Act that requires certain manufacturers of prescription drugs to annually collect and report information on payments or transfers of value to physicians and teaching hospitals, as well as ownership and investment interests held by physicians and their immediate family members. Manufacturers were required to begin collecting information on August 1, 2013, with the first reports due March 31, 2014. The reported data is posted in searchable form on a public website. Failure to submit required information may result in civil monetary penalties.

In addition, several states now require prescription drug companies to report expenses relating to the marketing and promotion of drug products and to report gifts and payments to individual healthcare practitioners and entities in these states. Other states prohibit various other marketing-related activities. Still other states require the posting of information relating to clinical studies and their outcomes. In addition, California, Connecticut, Nevada and Massachusetts require pharmaceutical companies to implement compliance programs and marketing codes. Several additional states are considering similar proposals. Some of the state laws are broader in scope than federal laws. Compliance with these laws is difficult and time consuming, and companies that do not comply with these state laws face civil penalties.

Reimbursement

Sales of any of our product candidates that are approved will depend, in part, on the extent to which the costs of our approved products will be covered by third-party payors, such as government health programs, commercial insurance and managed healthcare organizations. These third-party payors are increasingly challenging the prices charged for medical products and services. Additionally, the containment of healthcare costs has become a priority of federal and state governments and the prices of drugs have been a focus in this effort. The U.S. government, state legislatures and foreign governments have shown significant interest in implementing cost-containment programs, including price controls, restrictions on reimbursement and requirements for substitution of generic products. Adoption of price controls and cost-containment measures, and adoption of more restrictive policies in jurisdictions with existing controls and measures, could further limit our expected net revenue and results. If any of our products are approved and these third-party payors do not consider our approved products to be cost-effective compared to other therapies, they may not cover our approved products as a benefit under their plans or, if they do, the level of payment may not be sufficient to allow us to sell our approved products on a profitable basis.

The Medicare Prescription Drug, Improvement, and Modernization Act of 2003 (“MMA”), imposed new requirements for the distribution and pricing of prescription drugs for Medicare beneficiaries. Under Part D, Medicare beneficiaries may enroll in prescription drug plans offered by private entities which will provide coverage of outpatient prescription drugs. Part D plans include both stand-alone prescription drug benefit plans and prescription drug coverage as a supplement to Medicare Advantage plans. Unlike Medicare Part A and B, Part D coverage is not standardized. Part D prescription drug plan sponsors are not required to pay for all covered Part D drugs, and each drug plan can develop its own drug formulary that identifies which drugs it will cover and at what tier or level. However, Part D prescription drug formularies must include drugs within each therapeutic category and class of covered Part D drugs, though not necessarily all the drugs in each category or class. Any formulary used by a Part D prescription drug plan must be developed and reviewed by a pharmacy and therapeutic committee. Government payment for some of the costs of prescription drugs may increase demand for our products for which we receive marketing approval. However, any negotiated prices for our approved products covered by a Part D prescription drug plan will likely be lower than the prices we might otherwise obtain. Moreover, while the MMA applies only to drug benefits for Medicare beneficiaries, private payors often follow Medicare coverage policy and payment limitations in setting their own payment rates. Any reduction in payment that results from the MMA may result in a similar reduction in payments from non-governmental payors.

The American Recovery and Reinvestment Act of 2009 provides funding for the federal government to compare the effectiveness of different treatments for the same illness. A plan for the research will be developed by the Department of Health and Human Services, the Agency for Healthcare Research and Quality and the National Institutes for Health, and periodic reports on the status of the research and related expenditures will be made to the U.S. Congress. Although the results of the comparative effectiveness studies are not intended to mandate coverage policies for public or private payors, it is not clear what effect, if any, the research will have on the sales of any approved product, if any such product or the condition that it is intended to treat is the subject of a study. It is also possible that comparative effectiveness research demonstrating benefits in a competitor’s product could adversely affect the sales of our product candidates. If third-party payors do not consider our approved products to be cost-effective compared to other available therapies, they may not cover our approved products as a benefit under their plans or, if they do, the level of payment may not be sufficient to allow us to sell our approved products on a profitable basis.

The Affordable Care Act was enacted in March 2010, which includes measures to significantly change the way healthcare is financed by both governmental and private insurers. Among the provisions of the Affordable Care Act of importance to the pharmaceutical and biotechnology industry are the following:

- 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, that began in 2011;
- an increase in 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;

- a new Medicare Part D coverage gap discount program, in which manufacturers must agree to offer 50% 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;
- extension of manufacturers' Medicaid rebate liability to covered drugs dispensed to individuals who are enrolled in Medicaid managed care organizations;
- expansion of eligibility criteria for Medicaid programs by, among other things, allowing states to offer Medicaid coverage to additional individuals and by adding new mandatory eligibility categories for certain individuals with income at or below 133% of the Federal Poverty Level, thereby potentially increasing manufacturers' Medicaid rebate liability;
- expansion of the entities eligible for discounts under the Public Health Service pharmaceutical pricing program;
- expansion of healthcare fraud and abuse laws, including the False Claims Act and the Anti-Kickback Statute, new government investigative powers, and enhanced penalties for noncompliance;
- a licensure framework for follow-on biologic products;
- a new Patient-Centered Outcomes Research Institute to oversee, identify priorities in, and conduct comparative clinical effectiveness research, along with funding for such research;
- new requirements under the federal Open Payments program for drug manufacturers to report information related to payments and other transfers of value made to physicians and other healthcare providers as well as ownership or investment interests held by physicians and their immediate family members;
- a new requirement to annually report drug samples that manufacturers and distributors provide to physicians, effective April 1, 2012;
- creation of the Independent Payment Advisory Board which, beginning in 2014, will have authority to recommend certain changes to the Medicare program that could result in reduced payments for prescription drugs and those recommendations could have the effect of law even if Congress does not act on the recommendations; and
- establishment of a Center for Medicare Innovation at CMS to test innovative payment and service delivery models to lower Medicare and Medicaid spending, potentially including prescription drug spending that began on January 1, 2011.

In addition, in some non-U.S. jurisdictions, the proposed pricing for a product candidate must be approved before it may be lawfully marketed. The requirements governing drug pricing vary widely from country to country. For example, the European Union provides options for its member states to restrict the range of medicinal products for which their national health insurance systems provide reimbursement and to control the prices of medicinal products for human use. A member state may approve a specific price for the medicinal product or it may instead adopt a system of direct or indirect controls on the profitability of the company placing the medicinal product on the market. There can be no assurance that any country that has price controls or reimbursement limitations for pharmaceutical products will allow favorable reimbursement and pricing arrangements for any of our product candidates. Historically, product candidates launched in the European Union do not follow price structures of the United States and generally tend to be significantly lower.

It is uncertain whether there will be any legislation that will replace or amend the Affordable Care Act.

21st Century Cures Act

The 21st Century Cures Act, which the U.S. House of Representatives passed in July 2015 and President Obama signed into law in December 2016, provides for a wide range of reforms, such as broadening the types of data required to support drug approval, extending protections from genetic competition, accelerating approval of breakthrough therapies, expanding the orphan drug product program, and clarifying how manufacturers communicate about their products.

Employees

As of December 31, 2018, we had 10 employees, including 5 in product development and 5 in management or administrative positions. We also have engaged several independent consultants to support our organization.

Directors and Executive Officers

See Item 10 below for detailed information on our directors and executive officers. No family relationships exist among any of our directors or executive officers.

Corporate Information and History

We are a Delaware corporation that was originally incorporated in the State of Nevada on January 10, 1995. We reincorporated into the State of Delaware on June 18, 2015. Our corporate headquarters are located at 1317 Carlton Avenue, Suite 200, Charlottesville, Virginia 22902, our telephone number is (434) 220-0718, and our Internet web site address is www.diffusionpharma.com. The information contained on our web site or connected to our web site is not incorporated by reference into and should not be considered part of this annual report on Form 10-K.

Reverse Stock Split

On December 13, 2018, the Company filed a Certificate of Amendment to its Certificate of Incorporation with the Secretary of State of the State of Delaware to effect a 1-to-15 reverse stock split (the “Reverse Stock Split”) of the common stock. No fractional shares were issued in connection with the Reverse Stock Split. Stockholders who otherwise would have been entitled to receive fractional shares of common stock had their holdings rounded up to the next whole share. Proportional adjustments were made to the Company’s outstanding warrants, stock options and other equity securities and to the Company’s 2015 Equity Incentive Plan, as amended, to reflect the Reverse Stock Split, in each case, in accordance with the terms thereof. Unless the context otherwise requires, all share and per share amounts in this annual report on Form 10-K have been adjusted to reflect the Reverse Stock Split.

Available Information

We file electronically with the SEC annual reports on Form 10-K, quarterly reports on Form 10-Q, current reports on Form 8-K and amendments to those reports filed or furnished pursuant to Section 13 or 15(d) of the Securities Exchange Act of 1934. The SEC maintains an Internet site (www.sec.gov) that contains reports, proxy and information statements, and other information regarding issuers that file electronically with the SEC. Copies of these reports, proxy and information statements and other information may be obtained by electronic request at the following e-mail address: publicinfo@sec.gov. We make available, free of charge and through our Internet web site at www.diffusionpharma.com, our annual reports on Form 10-K, quarterly reports on Form 10-Q, current reports on Form 8-K and any amendments to any such reports filed or furnished pursuant to Section 13(a) or 15(d) of the Securities Exchange Act of 1934, as amended, as soon as reasonably practicable after we electronically file such material with, or furnish it to, the SEC. We also make available, free of charge and through our Internet web site, to any stockholder who requests, the charters of our board committees, our Corporate Governance Guidelines and our Code of Business Conduct and Ethics. Requests for copies can be directed to Investor Relations at (434) 220-0718.

Cautionary Note Regarding Forward-Looking Statements

This Annual Report on Form 10-K (this “Annual Report”) includes forward-looking statements. We may, in some cases, use terms such as “believes,” “estimates,” “anticipates,” “expects,” “plans,” “intends,” “may,” “could,” “might,” “will,” “should,” “approximately” or other words that convey uncertainty of future events or outcomes to identify these forward-looking statements. Forward-looking statements appear in a number of places throughout this Annual Report and include statements regarding our intentions, beliefs, projections, outlook, analyses or current expectations concerning, among other things, our ongoing and planned preclinical development and clinical trials, the timing of and our ability to make regulatory filings and obtain and maintain regulatory approvals for our product candidates, our intellectual property position, the degree of clinical utility of our products, particularly in specific patient populations, our ability to develop commercial functions, expectations regarding clinical trial data, our results of operations, cash needs, financial condition, liquidity, prospects, growth and strategies, the industry in which we operate and the trends that may affect the industry or us.

By their nature, forward-looking statements involve risks and uncertainties because they relate to events, competitive dynamics and industry change, and depend on the economic circumstances that may or may not occur in the future or may occur on longer or shorter timelines than anticipated. Although we believe that we have a reasonable basis for each forward-looking statement contained or incorporated by reference in this Annual Report, we caution you that forward-looking statements are not guarantees of future performance and that our actual results of operations, financial condition and liquidity, and the development of the industry in which we operate may differ materially from the forward-looking statements contained or incorporated by reference in this Annual Report. In addition, even if our results of operations, financial condition and liquidity, and the development of the industry in which we operate are consistent with the forward-looking statements contained or incorporated by reference in this Annual Report, they may not be predictive of results or developments in future periods.

Actual results could differ materially from our forward-looking statements due to a number of factors, including risks related to:

- our ability to obtain additional financing;
- our estimates regarding expenses, capital requirements and needs for additional financing;
- the success and timing of our preclinical studies and clinical trials;
- the difficulties in obtaining and maintaining regulatory approval of our products and product candidates, and the labeling under any approval we may obtain;
- our plans and ability to develop and commercialize our product candidates;
- our failure to recruit or retain key scientific or management personnel or to retain our executive officers;
- the accuracy of our estimates of the size and characteristics of the potential markets for our product candidates and our ability to serve those markets;
- regulatory developments in the United States and foreign countries;
- the rate and degree of market acceptance of any of our product candidates;
- obtaining and maintaining intellectual property protection for our product candidates and our proprietary technology;
- our ability to operate our business without infringing the intellectual property rights of others;
- recently enacted and future legislation regarding the healthcare system;
- our ability to maintain our listing on the Nasdaq Capital Market;
- our ability to continue as a going concern;
- the success of competing products that are or become available; and
- the performance of third parties, including contract research organizations and manufacturers.

You should also read carefully the factors described in the “Risk Factors” section of this Annual Report and elsewhere to better understand the risks and uncertainties inherent in our business and underlying any forward-looking statements. As a result of these factors, we cannot assure you that the forward-looking statements contained or incorporated by reference in this Annual Report will prove to be accurate. Furthermore, if our forward-looking statements prove to be inaccurate, the inaccuracy may be material. In light of the significant uncertainties in these forward-looking statements, you should not regard these statements as a representation or warranty by us or any other person that we will achieve our objectives and plans in any specified timeframe, or at all.

Any forward-looking statements that we make contained or incorporated by reference in this Annual Report speak only as of the date of such statement, and, except as required by applicable law, we undertake no obligation to update such statements to reflect events or circumstances after the date of this Annual Report or to reflect the occurrence of unanticipated events. Comparisons of results for current and any prior periods are not intended to express any future trends or indications of future performance, unless expressed as such, and should only be viewed as historical data.

ITEM 1A. RISK FACTORS

The following are significant factors known to us that could materially harm our business, operating results or financial condition or could cause our actual results to differ materially from our anticipated results or other expectations, including those expressed in any forward-looking statement made in this report:

Risks Related to Our Financial Needs

We have limited cash resources, have incurred significant losses since our inception and have a history of net losses and negative cash flow from operations.

We are a clinical-stage biotechnology company and, as a result, we have a limited operating history and there is little historical basis from which to assess how we will respond to competitive or economic challenges or other challenges to our business. Our business and prospects must be considered in light of the risks and uncertainties frequently encountered by similarly situated companies.

We have limited cash resources, have generated substantial net losses and negative cash flow from operations since our inception, and we continue to incur significant research, development and other expenses related to our ongoing operations for other product candidates. We expect to incur losses and negative cash flow for the foreseeable future. Our ability to generate sufficient revenues from our product candidates, if approved, will depend on numerous factors described in the following risk factors and elsewhere in this report. Even if we achieve profitability in the future, we may not be able to sustain profitability in subsequent periods. Our prior losses and expected future losses have had and will continue to have an adverse effect on our stockholders' equity.

We currently generate no revenue from the sale of products and may never become profitable.

To date, we have not generated any revenues from our product candidates. Even if we are able to successfully achieve regulatory approval for our product candidates, we do not know when any of these products will generate revenue for us, if at all. Our ability to generate revenue from our current product candidates or future products also depends on a number of additional factors, including our ability to:

- successfully complete development activities, including the necessary clinical trials;
- complete and submit NDAs to the FDA and obtain regulatory approval for indications for which there is a commercial market;
- complete and submit applications to, and obtain regulatory approval from, foreign regulatory authorities;
- develop a commercial organization capable of sales, marketing and distribution for the products we intend to sell ourselves in the markets in which we have retained commercialization rights; and
- find suitable distribution partners to help us market, sell and distribute our approved products in other markets.

In addition, because of the numerous risks and uncertainties associated with product development, including that our product candidates may not advance through development or achieve the endpoints of applicable clinical trials, we are unable to predict the timing or amount of increased expenses, or when or if we will be able to achieve or maintain profitability. Even if we are able to complete the process described above, we anticipate incurring significant costs associated with commercializing these products.

We will require additional capital to fund our operations which may not be available on acceptable terms or at all. If we fail to obtain necessary financing, we may be unable to complete the development and commercialization of our product candidates.

Our operations have consumed substantial amounts of cash since inception. We expect to continue to spend substantial amounts to advance the clinical development of our product candidates and to commercialize any product candidates for which we receive regulatory approval. At the current time, the bulk of our cash resources for clinical development is dedicated to the Phase 3 trial for TSC in inoperable GBM as well as the Phase 2 trial for TSC in stroke. While we believe we have adequate cash resources to continue operations into July 2019, we will need to raise additional funds in order to complete these trials. We do not expect to commence any clinical trials beyond these trials unless we are able to raise additional capital, enter into a strategic partnership, or make alternative financing arrangements for any such trial.

We cannot be certain that additional funding will be available on acceptable terms, or at all. Conditions in the capital markets and the financial services industry may make equity and debt financing more difficult to obtain, and may negatively impact our ability to complete financing transactions. To the extent that we raise additional funds by issuing equity securities, our stockholders may experience significant dilution. Any debt financing, if available, may involve restrictive covenants, such as limitations on our ability to incur additional indebtedness and other operating restrictions that could adversely impact our ability to conduct our business.

If we are unable to raise additional capital in sufficient amounts or on terms acceptable to us we may have to significantly delay, scale back or discontinue the development or commercialization of one or more of our product candidates or one or more of our other research and development initiatives. We also could be required to:

- seek collaborators for one or more of our current or future product candidates at an earlier stage than otherwise would be desirable or on terms that are less favorable than might otherwise be available; or
- relinquish or license on unfavorable terms our rights to technologies or product candidates that we otherwise would seek to develop or commercialize ourselves.

Our forecast of the period of time through which our financial resources will be adequate to support our operations is a forward-looking statement and involves risks and uncertainties, and actual results could vary as a result of a number of factors, including the factors discussed elsewhere in this “Risk Factors” section. We have based this estimate on assumptions that may prove to be wrong, and we could utilize our available capital resources sooner than we currently expect. Our future funding requirements, both near and long-term, will depend on many factors, including, but not limited to:

- the initiation, progress, timing, costs and results of clinical trials for our product candidates and any future product candidates we may in-license;
- the clinical development plans we establish for these product candidates;
- the number and characteristics of product candidates that we in-license and develop;
- the outcome, timing and cost of regulatory approvals by the FDA and comparable foreign regulatory authorities, including the potential for the FDA or comparable foreign regulatory authorities to require that we perform more studies than those that we currently expect;
- the cost of filing, prosecuting, defending and enforcing any patent claims and other intellectual property rights;
- the effect of competing technological and market developments; and
- the cost and timing of completion of becoming a commercial organization.

Raising additional capital through the capital markets or strategic partnerships may cause dilution to our existing stockholders, restrict our operations or require us to relinquish rights to our technologies or product candidates.

We may seek additional capital through a combination of private and public equity offerings, debt financings, receivables or royalty financings, strategic partnerships and alliances and licensing arrangements. We do not currently have any committed external source of funds. To the extent that we raise additional capital through the sale of equity or convertible debt securities, your ownership interest will be diluted, and the terms may include liquidation or other preferences that adversely affect the rights of existing stockholders. Debt, receivables and royalty financings may be coupled with an equity component, such as warrants to purchase stock, which could also result in dilution of our existing stockholders' 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 and may result in liens being placed on our assets and intellectual property. If we were to default on such indebtedness, we could lose such assets and intellectual property.

Also, we may raise additional funds through strategic partnerships and alliances and licensing arrangements with third parties. These strategic partnerships could take the form of a merger, a license of our product candidates or an outright sale of our product candidates. In connection with a strategic partnership, we may have to relinquish valuable rights to our product candidates, which could materially decrease any potential returns on our investment in our product candidates, or grant licenses on terms that are not favorable to us or are less favorable than we would have received upon completion of our product research and testing. Additionally, strategic partnerships could include equity issuances that dilute your ownership in us.

We have a history of operating losses and expect to continue to incur losses in the foreseeable future, which raises substantial doubt about our ability to continue as a going concern.

As discussed further in note 2 to our audited consolidated financial statements for the year ended December 31, 2018, we have a history of operating losses and expect to continue to incur losses in the foreseeable future, which raises substantial doubt regarding our ability to continue as a going concern. We currently have no sources of revenue and our ability to continue as a going concern is dependent on our ability to raise capital to fund our operations and future business plans. Additionally, volatility in the capital markets and general economic conditions in the United States may be a significant obstacle to raising the required funds. The consolidated financial statements do not include any adjustments that might be necessary should the Company be unable to continue as a going concern. If the going concern basis were not appropriate for these financial statements, adjustments would be necessary in the carrying value of assets and liabilities, the reported expenses and the balance sheet classifications used. If we are unable to continue as a going concern, our shareholders could suffer the loss of all or a substantial portion of their investment in us.

As described above, we believe we have adequate cash resources to continue operations into July 2019. In order to have sufficient cash to fund our operations beyond July 2019, we will need to raise additional equity or debt capital, or enter into a partnering transaction that provides liquidity to the Company, to continue as a going concern and we cannot provide any assurance that we will be successful in doing so.

Risks Related to Development, Regulatory Approval and Commercialization

Our business is dependent on the successful development, regulatory approval and commercialization of our product candidates, which include products primarily for the treatment of glioblastoma multiforme, and stroke.

Our portfolio of product candidates includes TSC, which is a novel small molecule that re-oxygenates hypoxic tissue, enhancing the efficacy of radiation and chemotherapy without harmful side effects which is in Phase 3 clinical development for glioblastoma multiforme. In addition, TSC may have potential applications in stroke, where we are beginning Phase 2 trials. The success of our business, including our ability to finance our company and generate any revenue in the future, primarily will depend on the successful development, regulatory approval and commercialization of our product candidates. In the future, we may also become dependent on one or more other product candidates or any future product candidates that we may in-license, acquire or develop. There have been many failures in drugs that other companies have tried to develop to treat the indications the company is or may be pursuing, including glioblastoma multiforme, stroke and other indications. There can be no assurance that the company will have success where others have failed.

The clinical and commercial success of our product candidates will depend on a number of factors, including the following:

- timely completion of our clinical trials, which may be significantly slower or cost more than we currently anticipate and will depend substantially upon the performance of third-party contractors;
- whether we are required by the FDA or similar foreign regulatory agencies to conduct additional clinical trials beyond those planned to support the approval and commercialization of our product candidates or any future product candidates;
- acceptance of our proposed indications and primary endpoint assessments relating to the proposed indications of our product candidates by the FDA and similar foreign regulatory authorities;
- our ability to demonstrate to the satisfaction of the FDA and similar foreign regulatory authorities, the safety and efficacy of our product candidates or any future product candidates;
- the prevalence, duration and severity of potential side effects experienced with our product candidates or future approved products, if any;
- the timely receipt of necessary marketing approvals from the FDA and similar foreign regulatory authorities;
- achieving and maintaining, and, where applicable, ensuring that our third-party contractors achieve and maintain, compliance with our contractual obligations and with all regulatory requirements applicable to our product candidates or any future product candidates or approved products, if any;
- the ability of third parties with whom we contract to manufacture clinical trial and commercial supplies of our product candidates or any future product candidates, remain in good standing with regulatory agencies and develop, validate and maintain commercially viable manufacturing processes that are compliant with cGMP;
- a continued acceptable safety profile during clinical development and following approval of our product candidates or any future product candidates;
- our ability to successfully commercialize our product candidates or any future product candidates in the United States and internationally, if approved for marketing, sale and distribution in such countries and territories, whether alone or in collaboration with others;
- acceptance by physicians and patients of the benefits, safety and efficacy of our product candidates or any future product candidates, if approved, including relative to alternative and competing treatments;
- our and our partners' ability to establish and enforce intellectual property rights in and to our product candidates or any future product candidates;
- our and our partners' ability to avoid third-party patent interference or intellectual property infringement claims; and
- our ability to in-license or acquire additional product candidates or commercial-stage products that we believe can be successfully developed and commercialized.

If we do not achieve one or more of these factors, many of which are beyond our control, in a timely manner or at all, we could experience significant delays or an inability to obtain regulatory approvals or commercialize our product candidates. Even if regulatory approvals are obtained, we may never be able to successfully commercialize any of our product candidates. Accordingly, we cannot assure you that we will be able to generate sufficient revenue through the sale of our product candidates or any future product candidates to continue our business.

Clinical drug development for our product candidates is very expensive, time-consuming and uncertain. Our clinical trials may fail to adequately demonstrate the safety and efficacy of our product candidates, which could prevent or delay regulatory approval and commercialization.

Clinical drug development for our product candidates is very expensive, time-consuming, difficult to design and implement and its outcome is inherently uncertain. Before obtaining regulatory approval for the commercial sale of a product candidate, we must demonstrate through clinical trials that a product candidate is both safe and effective for use in the target indication. Most product candidates that commence clinical trials are never approved by regulatory authorities for commercialization. Our product candidates are in early stages of development. We expect that clinical trials for these product candidates will take several years, but may take significantly longer than expected to complete. In addition, we, any partner with which we may in the future collaborate, the FDA, an IRB or other regulatory authorities, including state and local agencies and counterpart agencies in foreign countries, may suspend, delay, require modifications to or terminate our clinical trials at any time, for various reasons, including:

- discovery of serious or unexpected toxicities or side effects experienced by study participants or other safety issues;
- lack of effectiveness of any product candidate during clinical trials or the failure of our product candidates to meet specified endpoints;
- slower than expected rates of subject recruitment and enrollment rates in clinical trials resulting from numerous factors, including the prevalence of other companies' clinical trials for their product candidates for the same indication, or clinical trials for indications for which patients do not as commonly seek treatment;
- difficulty in retaining subjects who have initiated a clinical trial but may withdraw at any time due to adverse side effects from the therapy, insufficient efficacy, fatigue with the clinical trial process or for any other reason;
- difficulty in obtaining IRB approval for studies to be conducted at each site;
- delays in manufacturing or obtaining, or inability to manufacture or obtain, sufficient quantities of materials for use in clinical trials;
- inadequacy of or changes in our manufacturing process or the product formulation or method of delivery;
- changes in applicable laws, regulations and regulatory policies;
- delays or failure in reaching agreement on acceptable terms in clinical trial contracts or protocols with prospective clinical research organizations (“CROs”), clinical trial sites and other third-party contractors;
- inability to add a sufficient number of clinical trial sites;
- uncertainty regarding proper dosing;
- failure of our CROs or other third-party contractors to comply with contractual and regulatory requirements or to perform their services in a timely or acceptable manner;
- failure by us, our employees, our CROs or their employees or any partner with which we may collaborate or their employees to comply with applicable FDA or other regulatory requirements relating to the conduct of clinical trials or the handling, storage, security and recordkeeping for drug products;
- scheduling conflicts with participating clinicians and clinical institutions;

- failure to design appropriate clinical trial protocols;
- insufficient data to support regulatory approval;
- inability or unwillingness of medical investigators to follow our clinical protocols; or
- difficulty in maintaining contact with subjects during or after treatment, which may result in incomplete data.

We or any partner with which we may collaborate may suffer significant setbacks in our or their clinical trials similar to the experience of a number of other companies in the pharmaceutical and biotechnology industries, even after receiving promising results in earlier trials. In the event that we or our potential partners abandon or are delayed in the clinical development efforts related to our product candidates, we may not be able to execute on our business plan effectively and our business, financial condition, operating results and prospects would be harmed.

We may be unable to begin or complete our clinical trials or other product research due to our liquidity condition .

In the first quarter of 2018, we began dosing patients under the protocol permitted by the FDA with respect to our Phase 3 clinical study of TSC. Although enrollment and dosing has commenced, we have encountered some challenges in the early enrollment of patients in the study. Such delays could materially increase our costs of conducting the study and our time frame for potentially completing this study. There is no assurance that we will be able to complete this study or that the study will be completed in a timely or cost efficient manner. Currently, we do not anticipate receiving results for this trial until 2024, which time period could be delayed if we encounter further difficulties and/or delays in enrolling patients, opening additional clinical sites or other aspects of the study

Also, as described above, we believe we have adequate cash resources to continue operations into July 2019. In order to have sufficient cash to fund our operations, including our product research, development and testing beyond July 2019, we will need to raise additional equity or debt capital, or enter into a partnering transaction that provides liquidity to the Company. Notably, we intend to commence the Phase 2 clinical study on TSC for its potential treatment of strokes, however, we will require additional liquidity to complete this trial and delays in receiving financing could potentially delay the beginning of or the overall speed of this proposed trial. Failure to obtain additional material liquidity could further delay our ongoing product development efforts, including delaying future clinical trials of TSC. Any of the foregoing could have a negative impact on our business, financial condition or prospects.

We may be unable to obtain regulatory approval for TSC or our other future product candidates for the indications of which we are seeking under applicable regulatory requirements. The FDA and foreign regulatory bodies have substantial discretion in the approval process, including the ability to delay, limit or deny approval of product candidates. The delay, limitation or denial of any regulatory approval would adversely impact commercialization, our potential to generate revenue, our business and our operating results.

We currently have no products approved for sale, and we may never obtain regulatory approval to commercialize any of our current or future product candidates. The research, testing, manufacturing, safety surveillance, efficacy, quality control, recordkeeping, labeling, packaging, storage, approval, sale, marketing, distribution, import, export, and reporting of safety and other post-market information related to our drug products are subject to extensive regulation by the FDA and other regulatory authorities in the United States and in foreign countries, and such regulations differ from country to country. We are not permitted to market any of our current product candidates in the United States until we receive approval of an NDA or other applicable regulatory filing from the FDA. We are also not permitted to market any of our current product candidates in any foreign countries until we receive the requisite approval from the applicable regulatory authorities of such countries.

To gain approval to market a new drug, such as TSC, the FDA and foreign regulatory authorities must receive preclinical and clinical data that adequately demonstrate the safety, purity, potency, efficacy and compliant manufacturing of the product for the intended indication applied for in an NDA or other applicable regulatory filing. The development and approval of new drug products involves a long, expensive and uncertain process, and delay or failure can occur at any stage. A number of companies in the pharmaceutical and biopharmaceutical industry have suffered significant setbacks in clinical trials, including in Phase 3 clinical development, even after promising results in earlier preclinical studies or clinical trials. These setbacks have been caused by, among other things, findings made while clinical trials were underway and safety or efficacy observations made in clinical trials, including previously unreported adverse events. Success in preclinical testing and early clinical trials does not ensure that later clinical trials will be successful, and the results of clinical trials by other parties may not be indicative of the results in trials we or our partners may conduct.

The FDA and foreign regulatory bodies have substantial discretion in the drug approval process, including the ability to delay, limit or deny approval of product candidates for many reasons, including:

- the FDA or the applicable foreign regulatory body may disagree with the design or implementation of one or more clinical trials;
- the FDA or the applicable foreign regulatory body may not deem a product candidate safe and effective for its proposed indication, or may deem a product candidate's safety or other perceived risks to outweigh its clinical or other benefits;
- the FDA or the applicable foreign regulatory body may not find the data from preclinical studies and clinical trials sufficient to support approval, or the results of clinical trials may not meet the level of statistical or clinical significance required by the FDA or the applicable foreign regulatory body for approval;
- the FDA or the applicable foreign regulatory body may disagree with our interpretation of data from preclinical studies or clinical trials performed by us or third parties, or with the interpretation of any partner with which we may collaborate;
- the data collected from clinical trials may not be sufficient to support the submission of an NDA or other applicable regulatory filing;
- the FDA or the applicable foreign regulatory body may require additional preclinical studies or clinical trials;
- the FDA or the applicable foreign regulatory agency may identify deficiencies in the formulation, quality control, labeling or specifications of our current or future product candidates;
- the FDA or the applicable foreign regulatory agency may require clinical trials in pediatric patients in order to establish pharmacokinetics or safety for this more drug-sensitive population;
- the FDA or the applicable foreign regulatory agency may grant approval contingent on the performance of costly additional post-approval clinical trials;
- the FDA or the applicable foreign regulatory agency also may approve our current or any future product candidates for a more limited indication or a narrower patient population than we originally requested;
- the FDA or applicable foreign regulatory agency may not approve the labeling that we believe is necessary or desirable for the successful commercialization of our product candidates;
- the FDA or the applicable foreign regulatory body may not approve of the manufacturing processes, controls or facilities of third-party manufacturers or testing labs with which we contract; or
- the FDA or the applicable foreign regulatory body may change its approval policies or adopt new regulations in a manner rendering our clinical data or regulatory filings insufficient for approval.

Of the large number of drugs in development, only a small percentage successfully complete the FDA or other regulatory approval processes and are commercialized. Our product candidates may not be approved by the FDA or applicable foreign regulatory agencies even if they meet specified endpoints in our clinical trials. The FDA or applicable foreign regulatory agencies may ask us to conduct additional costly and time-consuming clinical trials in order to obtain marketing approval or approval to enter into an advanced phase of development, or may change the requirements for approval even after such agency has reviewed and commented on the design for the clinical trials.

Additionally, current governmental conditions, such as a future shutdown of the U.S. government or potential complications from the United Kingdom's proposed exit from the European Union, could potentially delay the review and approval of any drugs submitted to the FDA or applicable foreign regulatory agencies,

Any delay in obtaining, or inability to obtain, applicable regulatory approval for any of our product candidates would delay or prevent commercialization of our product candidates and would harm our business, financial condition, operating results and prospects.

Even if our product candidates obtain regulatory approval, they may fail to achieve the broad degree of physician and patient adoption and use necessary for commercial success.

The commercial success of any of our current or future product candidates, if approved, will depend significantly on the broad adoption and use of the resulting product by physicians and patients for approved indications, and may not be commercially successful. The degree and rate of physician and patient adoption of our current or future product candidates, if approved, will depend on a number of factors, including:

- the clinical indications for which the product is approved and patient demand for approved products that treat those indications;
- the effectiveness of our product as compared to other available therapies;
- the availability of coverage and adequate reimbursement from managed care plans and other healthcare payors for any of our product candidates that may be approved;
- the cost of treatment with our product candidates in relation to alternative treatments and willingness to pay for the product, if approved, on the part of patients;
- acceptance by physicians, major operators of clinics and patients of the product as a safe and effective treatment;
- physician and patient willingness to adopt a new therapy over other available therapies to treat approved indications;
- overcoming any biases physicians or patients may have toward particular therapies for the treatment of approved indications;
- proper training and administration of our product candidates by physicians and medical staff;
- patient satisfaction with the results and administration of our product candidates and overall treatment experience;
- the willingness of patients to pay for certain of our product candidates relative to other discretionary items, especially during economically challenging times;
- the revenue and profitability that our product candidate may offer a physician as compared to alternative therapies;
- the prevalence and severity of side effects;
- limitations or warnings contained in the FDA-approved labeling for our product candidates;
- any FDA requirement to undertake a REMS;

- the effectiveness of our sales, marketing and distribution efforts;
- adverse publicity about our product candidates or favorable publicity about competitive products; and
- potential product liability claims.

Our product candidates, if approved, will face significant competition and our failure to effectively compete may prevent us from achieving significant market penetration.

The pharmaceutical industry is characterized by rapidly advancing technologies, intense competition and a strong emphasis on developing proprietary therapeutics. Numerous companies are engaged in the development, patenting, manufacturing and marketing of health care products competitive with those that we are developing. We face competition from a number of sources, such as pharmaceutical companies, generic drug companies, biotechnology companies and academic and research institutions, many of which have greater financial resources, marketing capabilities, sales forces, manufacturing capabilities, research and development capabilities, clinical trial expertise, intellectual property portfolios, experience in obtaining patents and regulatory approvals for product candidates and other resources than us. Some of the companies that offer competing products also have a broad range of other product offerings, large direct sales forces and long-term customer relationships with our expected target physicians, which could inhibit our market penetration efforts.

Many pharmaceutical companies currently offer products, and continue to develop additional alternative product candidates and technologies, for indications similar to those targeted by our product candidates. We anticipate that, if we obtain regulatory approval of any of our product candidates, we will face significant competition from other approved therapies. If approved, our product candidates may also compete with unregulated, unapproved and off-label treatments. Certain of our product candidates, if approved, will present novel therapeutic approaches for the approved indications and will have to compete with existing therapies, some of which are widely known and accepted by physicians and patients. To compete successfully in this market, we will have to demonstrate that the relative cost, safety and efficacy of our products, when and if approved, provide an attractive alternative to existing and other new therapies. Such competition could lead to reduced market share for our product candidates and contribute to downward pressure on the pricing of our product candidates, which could harm our business, financial condition, operating results and prospects. For more information about the competition we face, see “Business—Competition.”

Additionally, our product candidates may affect our ability to sell that product candidate into higher priced markets. For example, TSC is currently being tested or proposed to be tested as a drug for various treatments. If TSC is approved as a treatment for multiple medical conditions, its pricing may be driven downwards to compete in the market for its lowest cost indication, which could potentially lower our potential revenues from TSC even if it is found to be an effective treatment for multiple medical conditions.

Due to less stringent regulatory requirements in certain foreign countries, there are many more products and procedures available for use in those international markets than are approved for use in the United States. In certain international markets, there are also fewer limitations on the claims that our competitors can make about the effectiveness of their products and the manner in which they can market them. As a result, we expect to face more competition in these markets than in the United States.

Any product candidates that we commercialize, or that any partner with which we may collaborate commercializes, will be subject to ongoing and continued regulatory review.

Even after we or our partners achieve U.S. regulatory approval for a product candidate, if any, we or our partners will be subject to continued regulatory review and compliance obligations. For example, with respect to our product candidates, the FDA may impose significant restrictions on the approved indicated uses for which the product may be marketed or on the conditions of approval. A product candidate’s approval may contain requirements for potentially costly post-approval studies and surveillance, including Phase 4 clinical trials or a REMS, to monitor the safety and efficacy of the product. We will also be subject to ongoing FDA obligations and continued regulatory review with respect to, among other things, the manufacturing, processing, labeling, packaging, distribution, adverse event reporting, storage, advertising, promotion and recordkeeping for our product candidates. These requirements include submissions of safety and other post-marketing information and reports, registration, as well as continued compliance with cGMP requirements and with the FDA’s GCP requirements and good laboratory practice (“GLP”) requirements, which are regulations and guidelines enforced by the FDA for all of our product candidates in clinical and preclinical development, and for any clinical trials that we conduct post-approval. To the extent that a product candidate is approved for sale in other countries, we may be subject to similar restrictions and requirements imposed by laws and government regulators in those countries.

In addition, manufacturers of drug products and their facilities are subject to continual review and periodic inspections by the FDA and other regulatory authorities for compliance with cGMP regulations. If we or a regulatory agency discovers previously unknown problems with a product, such as adverse events of unanticipated severity or frequency, or problems with the facility where, or processes by which, the product is manufactured, a regulatory agency may impose restrictions on that product or us, including requesting that we initiate a product recall, or requiring notice to physicians, withdrawal of the product from the market or suspension of manufacturing.

If we, our product candidates or the manufacturing facilities for our product candidates fail to comply with applicable regulatory requirements, a regulatory agency may:

- impose restrictions on the marketing or manufacturing of the product, suspend or withdraw product approvals or revoke necessary licenses;
- mandate modifications to promotional materials or require us to provide corrective information to healthcare practitioners;
- require us or our partners to enter into a consent decree, which can include imposition of various fines, reimbursements for inspection costs, required due dates for specific actions and penalties for noncompliance;
- issue warning letters, show cause notices or untitled letters describing alleged violations, which may be publicly available;
- commence criminal investigations and prosecutions;
- impose injunctions, suspensions or revocations of necessary approvals or other licenses;
- impose other civil or criminal penalties;
- suspend any ongoing clinical trials;
- delay or refuse to approve pending applications or supplements to approved applications filed by us or our potential partners;
- refuse to permit drugs or precursor chemicals to be imported or exported to or from the United States;
- suspend or impose restrictions on operations, including costly new manufacturing requirements; or
- seize or detain products or require us or our partners to initiate a product recall.

The regulations, policies or guidance of the FDA and other applicable government agencies may change and new or additional statutes or government regulations may be enacted that could prevent or delay regulatory approval of our product candidates or further restrict or regulate post-approval activities. We cannot predict the likelihood, nature or extent of adverse government regulation that may arise from future legislation or administrative action, either in the United States or abroad. If we are not able to achieve and maintain regulatory compliance, we may not be permitted to market our product candidates, which would adversely affect our ability to generate revenue and achieve or maintain profitability.

We have conducted and may in the future conduct clinical trials for our product candidates outside the United States and the FDA and applicable foreign regulatory authorities may not accept data from such trials.

We have conducted and may in the future choose to conduct one or more of our clinical trials outside the United States. Although the FDA or applicable foreign regulatory authority may accept data from clinical trials conducted outside the United States or the applicable jurisdiction, acceptance of such study data by the FDA or applicable foreign regulatory authority may be subject to certain conditions. Where data from foreign clinical trials are intended to serve as the basis for marketing approval in the United States, the FDA will not approve the application on the basis of foreign data alone unless those data are applicable to the U.S. population and U.S. medical practice; the studies were performed by clinical investigators of recognized competence; and the data are considered valid without the need for an on-site inspection by the FDA or, if the FDA considers such an inspection to be necessary, the FDA is able to validate the data through an on-site inspection or other appropriate means. Many foreign regulatory bodies have similar requirements. In addition, such foreign studies would be subject to the applicable local laws of the foreign jurisdictions where the studies are conducted. There can be no assurance the FDA or applicable foreign regulatory authority will accept data from trials conducted outside of the United States or the applicable jurisdiction. If the FDA or applicable foreign regulatory authority does not accept such data, it would likely result in the need for additional trials, which would be costly and time-consuming and delay aspects of our business plan.

Our product candidates may cause undesirable side effects or have other unexpected properties that could delay or prevent their regulatory approval, limit the commercial profile of an approved label or result in post-approval regulatory action.

Unforeseen side effects from any of our product candidates could arise either during clinical development or, if approved, after the approved product has been marketed. Undesirable side effects caused by product candidates could cause us, any partners with which we may collaborate or regulatory authorities to interrupt, modify, delay or halt clinical trials and could result in a more restrictive label or the delay or denial of regulatory approval by the FDA or comparable foreign authorities. In such an event, trials could be suspended or terminated and the FDA or comparable foreign regulatory authorities could order us, or our potential partners, to cease further development of or deny approval of product candidates for any or all targeted indications. The drug-related side effects could affect patient recruitment or the ability of enrolled patients to complete the trial or result in product liability claims. Any of these occurrences may harm our business, financial condition, operating results and prospects.

Additionally, if we or others identify undesirable side effects, or other previously unknown problems, caused by our product candidates after obtaining U.S. or foreign regulatory approval or other products with the same or related active ingredients, a number of potentially negative consequences could result, including:

- regulatory authorities may withdraw their approval of the product;
- regulatory authorities may require a recall of the product or we or our potential partners may voluntarily recall a product;
- regulatory authorities may require the addition of warnings or contraindications in the product labeling, narrowing of the indication in the product label or field alerts to physicians and pharmacies;
- we may be required to create a medication guide outlining the risks of such side effects for distribution to patients or institute a REMS;
- we may have limitations on how we promote the product;
- we may be required to change the way the product is administered or modify the product in some other way;

- the FDA or applicable foreign regulatory authority may require additional clinical trials or costly post-marketing testing and surveillance to monitor the safety or efficacy of the product;
- sales of the product may decrease significantly;
- we could be sued and held liable for harm caused to patients; and
- our brand and reputation may suffer.

Any of the above events resulting from undesirable side effects or other previously unknown problems could prevent us or our potential partners from achieving or maintaining market acceptance of the affected product candidate and could substantially increase the costs of commercializing our product candidates.

Because the results of preclinical studies and early-stage clinical trials are not necessarily predictive of future results, any product candidate we advance into additional clinical trials may not continue to have favorable results or receive regulatory approval.

Success in preclinical studies and early clinical trials does not ensure that later clinical trials will generate adequate data to demonstrate the efficacy and safety of an investigational drug. Many companies in the pharmaceutical and biotechnology industries, including those with greater resources and experience, have suffered significant setbacks in clinical trials, even after reporting promising results in earlier clinical trials. We do not know whether the clinical trials we may conduct will demonstrate adequate efficacy and safety or otherwise provide adequate information to result in regulatory approval to market any of our product candidates in any particular jurisdiction. If later-stage clinical trials do not produce favorable results, our ability to achieve regulatory approval for any of our product candidates may be compromised.

We may face product liability exposure, and if successful claims are brought against us, we may incur substantial liability if our insurance coverage for those claims is inadequate.

We face an inherent risk of product liability as a result of the clinical testing of our product candidates and will face an even greater risk if we commercialize any products. This risk exists even if a product is approved for commercial sale by the FDA and manufactured in facilities licensed and regulated by the FDA or an applicable foreign regulatory authority. Our products and product candidates are designed to affect important bodily functions and processes. Any side effects, manufacturing defects, misuse or abuse associated with our product candidates could result in injury to a patient or even death. We cannot offer any assurance that we will not face product liability suits in the future, nor can we assure you that our insurance coverage will be sufficient to cover our liability under any such cases.

In addition, a liability claim may be brought against us even if our product candidates merely appear to have caused an injury. Product liability claims may be brought against us by consumers, health care providers, pharmaceutical companies or others selling or otherwise coming into contact with our product candidates, among others. If we cannot successfully defend ourselves against product liability claims we will incur substantial liabilities and reputational harm. In addition, regardless of merit or eventual outcome, product liability claims may result in:

- withdrawal of clinical trial participants;
- termination of clinical trial sites or entire trial programs;
- the inability to commercialize our product candidates;
- decreased demand for our product candidates;
- impairment of our business reputation;

- product recall or withdrawal from the market or labeling, marketing or promotional restrictions;
- substantial costs of any related litigation or similar disputes;
- distraction of management’s attention and other resources from our primary business;
- substantial monetary awards to patients or other claimants against us that may not be covered by insurance; or
- loss of revenue.

We have obtained product liability insurance coverage for our clinical trials. However, large judgments have been awarded in class action or individual lawsuits based on drugs that had unanticipated side effects and our insurance coverage may not be sufficient to cover all of our product liability related expenses or losses and may not cover us for any expenses or losses we may suffer. Moreover, insurance coverage is becoming increasingly expensive, and, in the future, we may not be able to maintain insurance coverage at a reasonable cost, in sufficient amounts or upon adequate terms to protect us against losses due to product liability. We will need to increase our product liability coverage if any of our product candidates receive regulatory approval, which will be costly, and we may be unable to obtain this increased product liability insurance on commercially reasonable terms, or at all. A successful product liability claim or series of claims brought against us could cause our stock price to decline and, if judgments exceed our insurance coverage, could decrease our cash and could harm our business, financial condition, operating results and prospects.

If any of our product candidates are approved for marketing and we are found to have improperly promoted off-label uses, or if physicians misuse our products or use our products off-label, we may become subject to prohibitions on the sale or marketing of our products, product liability claims and significant fines, penalties and sanctions, and our brand and reputation could be harmed.

The FDA and other regulatory agencies strictly regulate the marketing and promotional claims that are made about drug products. In particular, a product may not be promoted for uses or indications that are not approved by the FDA or such other regulatory agencies as reflected in the product’s approved labeling and comparative safety or efficacy claims cannot be made without direct comparative clinical data. If we are found to have promoted off-label uses of any of our product candidates, we may receive warning or untitled letters and become subject to significant liability, which would materially harm our business. Both federal and state governments have levied large civil and criminal fines against companies for alleged improper promotion and have enjoined several companies from engaging in off-label promotion. If we become the target of such an investigation or prosecution based on our marketing and promotional practices, we could face similar sanctions, which would materially harm our business. In addition, management’s attention could be diverted from our business operations, significant legal expenses could be incurred and our brand and reputation could be damaged. The FDA has also requested that companies enter into consent decrees or permanent injunctions under which specified promotional conduct is changed or curtailed. If we are deemed by the FDA to have engaged in the promotion of our products for off-label use, we could be subject to FDA regulatory or enforcement actions, including the issuance of an untitled letter, a warning letter, injunction, seizure, civil fine or criminal penalties. It is also possible that other federal, state or foreign enforcement authorities might take action if they consider our business activities constitute promotion of an off-label use, which could result in significant penalties, including criminal, civil or administrative penalties, damages, fines, disgorgement, exclusion from participation in government healthcare programs and the curtailment or restructuring of our operations.

We cannot, however, prevent a physician from using our product candidates outside of those indications for use when in the physician’s independent professional medical judgment he or she deems appropriate. Physicians may also misuse our product candidates or use improper techniques, potentially leading to adverse results, side effects or injury, which may lead to product liability claims. If our product candidates are misused or used with improper technique, we may become subject to costly litigation by physicians or their patients. Furthermore, the use of our product candidates for indications other than those cleared by the FDA may not effectively treat such conditions, which could harm our reputation among physicians and patients.

We may choose not to continue developing or commercializing any of our product candidates at any time during development or after approval, which would reduce or eliminate our potential return on investment for those product candidates.

At any time, we may decide to discontinue the development of any of our product candidates or not to continue commercializing one or more of our approved product candidates for a variety of reasons, including changes in our internal product, technology or indication focus, the appearance of new technologies that make our product obsolete, competition from a competing product or changes in or failure to comply with applicable regulatory requirements. If we terminate a program in which we have invested significant resources, we will not receive any return on our investment and we will have missed the opportunity to have allocated those resources to potentially more productive uses.

We or our prospective partners may be subject to product recalls in the future that could harm our brand and reputation and could negatively affect our business.

We or our prospective partners may be subject to product recalls, withdrawals or seizures if any of our product candidates, if approved for marketing, fail to meet specifications or are believed to cause injury or illness or if we are alleged to have violated governmental regulations including those related to the manufacture, labeling, promotion, sale or distribution. Any recall, withdrawal or seizure in the future could materially and adversely affect consumer confidence in our brands and lead to decreased demand for our approved products. In addition, a recall, withdrawal or seizure of any of our approved products would require significant management attention, would likely result in substantial and unexpected expenditures and would harm our business, financial condition and operating results.

If we or any partners with which we may collaborate are unable to achieve and maintain coverage and adequate levels of reimbursement for any of our product candidates for which we receive regulatory approval, or any future products we may seek to commercialize, their commercial success may be severely hindered.

For any of our product candidates that become available only by prescription, successful sales by us or by any partners with which we may collaborate depend on the availability of coverage and adequate reimbursement from third-party payors. 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. The availability of coverage and adequate reimbursement from governmental healthcare programs, such as Medicare and Medicaid, and private third-party payors is critical to new product acceptance. Coverage decisions may depend upon clinical and economic standards that disfavor new drug products when more established or lower cost therapeutic alternatives are already available or subsequently become available. If any of our product candidates do not demonstrate attractive efficacy profiles, they may not qualify for coverage and reimbursement. Even if we obtain coverage for a given product, the resulting reimbursement payment rates might not be adequate or may require co-payments that patients find unacceptably high. 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.

In addition, the market for our product candidates will depend significantly on access to third-party payors' drug formularies, or lists of medications for which third-party payors provide coverage and reimbursement. The industry competition to be included in such formularies often leads to downward pricing pressures on pharmaceutical companies. Also, third-party payors may refuse to include a particular branded drug in their formularies or otherwise restrict patient access to a branded drug when a less costly generic equivalent or other alternative is available.

Third-party payors, whether foreign or domestic, or governmental or commercial, are developing increasingly sophisticated methods of controlling healthcare costs. In addition, in the United States, although private third-party payors tend to follow Medicare, 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 product candidates to each payor separately, with no assurance that coverage and adequate reimbursement will be obtained.

Further, we believe that future coverage and reimbursement will likely be subject to increased restrictions both in the United States and in international markets. Third-party coverage and reimbursement for any of our product candidates for which we may receive regulatory approval may not be available or adequate in either the United States or international markets, which could harm our business, financial condition, operating results and prospects.

We operate in a highly regulated industry such that the potential for legislative reform provides uncertainty and potential threats to our operating models and results.

In the United States, there have been, and we expect there will continue to be, a number of legislative and regulatory changes to the healthcare system that could affect our future revenue and profitability and the future revenue and profitability of any partner with which we may collaborate. Federal and state lawmakers regularly propose and, at times, enact legislation that results in significant changes to the healthcare system, some of which are intended to contain or reduce the costs of medical products and services. For example, in March 2010, President Obama signed one of the most significant healthcare reform measures in decades the Patient Protection and Affordable Care Act, as amended by the Health Care and Education Affordability Reconciliation Act of 2010, collectively referred to as the Affordable Care Act. It contains a number of provisions, including those governing enrollment in federal healthcare programs, reimbursement changes and fraud and abuse measures, all of which are expected to impact existing government healthcare programs and result in the development of new programs. The Affordable Care Act, among other things, (1) increased the minimum Medicaid rebates owed by most manufacturers under the Medicaid Drug Rebate Program and extended the rebate program to certain individuals enrolled in Medicaid managed care organizations, (2) established annual fees on manufacturers of certain branded prescription drugs and (3) enacted a Medicare Part D coverage gap discount program, in which manufacturers must agree to offer 50% point-of-sale discounts off negotiated prices of applicable brand drugs to eligible beneficiaries during their coverage gap period, as a condition for the manufacturer's outpatient drugs to be covered under Medicare Part D.

In addition, other legislative changes have been proposed and adopted in the United States since the Affordable Care Act was enacted. On August 2, 2011, the Budget Control Act of 2011, among other things, created measures for spending reductions by Congress. A Joint Select Committee on Deficit Reduction, tasked with recommending a targeted deficit reduction of at least \$1.2 trillion for the years 2013 through 2021, was unable to reach required goals, thereby triggering the legislation's automatic reduction to several government programs. This includes aggregate reductions of Medicare payments to providers up to 2% per fiscal year, which went into effect on April 1, 2013. On January 2, 2013, President Obama signed into law the American Taxpayer Relief Act of 2012, which, among other things, further reduced Medicare payments to several providers, including hospitals and imaging centers.

Further, the Protecting Access to Medicare Act of 2014, signed into law in April 2014, provides for a 0.5% change from 2013 federal payment rates under the Medicare Physician Fee Schedule through 2014 and a 0% update from January 1 until April 1, 2015. Congressional failure to intervene to prevent these changes in payment rates may adversely affect our future revenue and operating results. The 21st Century Cures Act, which the U.S. House of Representatives passed in July 2015 and President Obama signed into law in December 2016, provides a wide range of reforms, such as broadening the types of data required to support drug approval, extending protections from genetic competition, accelerating approval of breakthrough therapies, expanding the orphan drug product program, and clarifying how manufacturers communicate about their products.

Additionally, in January 2019, the Trump administration proposed a regulation to drastically change how prescription drugs are priced and paid for under Medicare. The proposed regulation is designed to reduce or eliminate rebates from drug manufacturers to pharmacy benefit managers and would push price discounts direct to consumers. It is currently unclear what the final form of the proposed regulation will be or if the regulation will go into effect, therefore, the extent to which any such changes may impact our business or financial condition is uncertain.

Additional state and federal healthcare reform measures may be adopted in the future, any of which could limit the amounts that federal and state governments will pay for healthcare products and services, which could result in reduced demand for our products once approved or additional pricing pressures.

Since its enactment, there have been judicial and Congressional challenges to certain aspects of the Affordable Care Act, and we expect there will be additional challenges and amendments to the Affordable Care Act in the future. The Trump administration and members of the U.S. Congress have indicated that they may continue to seek to modify, repeal, or otherwise invalidate all, or certain provisions of, the Affordable Care Act. In 2017, the Tax Cuts and Jobs Acts was enacted, which, among other things, removes penalties for not complying with the individual mandate to carry health insurance. It is uncertain the extent to which any such changes may impact our business or financial condition.

In addition, we cannot predict the likelihood, nature or extent of government regulation that may arise from future legislation or administrative or executive action, either in the United States or abroad. For example, certain policies of the Trump administration may impact our business and industry. Namely, the Trump administration has taken several executive actions, including the issuance of a number of Executive Orders, that could impose significant burdens on, or otherwise materially delay, the FDA's ability to engage in routine regulatory and oversight activities such as implementing statutes through rulemaking, issuance of guidance, and review and approval of marketing applications. Notably, on January 30, 2017, President Trump issued an Executive Order, applicable to all executive agencies, including the FDA, which requires that for each notice of proposed rulemaking or final regulation to be issued in fiscal year 2017, the agency shall identify at least two existing regulations to be repealed, unless prohibited by law. If these executive actions or future executive actions impose constraints on the FDA's ability to engage in oversight and implementation activities in the normal course, our business may be negatively impacted

We may also be subject to healthcare laws, regulation and enforcement and our failure to comply with those laws could adversely affect our business, operations and financial condition.

Certain federal and state healthcare laws and regulations pertaining to fraud and abuse and patients' rights are and will be applicable to our business. We are subject to regulation by both the federal government and the states in which we or our partners conduct our business. The laws and regulations that may affect our ability to operate include:

- the federal Anti-Kickback Statute, which prohibits, among other things, any person or entity from knowingly and willfully offering, soliciting, receiving or providing any remuneration (including any kickback, bribe or rebate), directly or indirectly, overtly or covertly, in cash or in kind, to induce either the referral of an individual or in return for the purchase, lease, or order of any good, facility item or service, for which payment may be made, in whole or in part, under federal healthcare programs such as the Medicare and Medicaid programs;
- federal civil and criminal false claims laws and civil monetary penalty laws, including, for example, the federal civil False Claims Act, which impose criminal and civil penalties, including civil whistleblower or qui tam actions, against individuals or entities for, among other things, knowingly presenting, or causing to be presented, to the federal government, including the Medicare and Medicaid programs, claims for payment that are false or fraudulent or making a false statement to avoid, decrease or conceal an obligation to pay money to the federal government;
- the federal Health Insurance Portability and Accountability Act of 1996 (“HIPAA”), which created new federal criminal statutes that prohibit knowingly and willfully executing, or attempting to execute, a scheme to defraud any healthcare benefit program or obtain, by means of false or fraudulent pretenses, representations or promises, any of the money or property owned by, or under the custody or control of, any healthcare benefit program, regardless of the payor (e.g., public or private), knowingly and willfully embezzling or stealing from a health care benefit program, willfully obstructing a criminal investigation of a health care offense and knowingly and willfully falsifying, concealing or covering up by any trick or device a material fact or making any materially false statements in connection with the delivery of, or payment for, healthcare benefits, items or services relating to healthcare matters;

- HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act, and their implementing regulations, which impose obligations on covered entities, including healthcare providers, health plans, and healthcare clearinghouses, as well as their respective business associates that create, receive, maintain or transmit individually identifiable health information for or on behalf of a covered entity, with respect to safeguarding the privacy, security and transmission of individually identifiable health information;
- the federal physician sunshine requirements under the Affordable Care Act, which require manufacturers of drugs, devices, biologics and medical supplies to report annually to the Centers for Medicare & Medicaid Services information related to payments and other transfers of value provided to physicians and teaching hospitals, and ownership and investment interests held by physicians and their immediate family members; and
- state law equivalents of each of the above federal laws, such as anti-kickback and false claims laws, which may apply to items or services reimbursed by any third-party payor, including commercial insurers; state laws that require pharmaceutical companies to comply with the pharmaceutical industry's voluntary compliance guidelines and the applicable compliance guidance promulgated by the federal government, or otherwise restrict payments that may be provided to healthcare providers and other potential referral sources; state laws that require drug manufacturers to report information related to payments and other transfers of value to healthcare providers or marketing expenditures; and 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.

Additional health care reform legislation further strengthened these laws. For example, the Affordable Care Act, among other things, amended the intent requirement of the federal Anti-Kickback Statute and certain criminal healthcare fraud statutes. A person or entity no longer needs to have actual knowledge of the statute or specific intent to violate it. In addition, the Affordable Care Act provided that the government may assert that a claim including items or services resulting from a violation of the federal Anti-Kickback Statute constitutes a false or fraudulent claim for purposes of the federal civil False Claims Act. Also, as noted above, in January 2019, the Trump administration proposed amending the Anti-Kickback Statute through an executive order to drastically change how prescription drugs are priced and paid for under Medicare. The proposed rule would, among other things, remove safe harbors for drug manufacturer discounts and rebates to pharmacy benefit managers.

Achieving and sustaining compliance with these laws may prove costly. In addition, any action against us for violation of these laws, 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. If our operations are found to be in violation of any of the laws described above or any other governmental laws or regulations that apply to us, we may be subject to penalties, including administrative, civil and criminal penalties, damages, fines, disgorgement, the exclusion from participation in federal and state healthcare programs, individual imprisonment or the curtailment or restructuring of our operations, any of which could adversely affect our ability to operate our business and our financial results.

Our employees, independent contractors, principal investigators, consultants, vendors, CROs and any partners with which we may collaborate may engage in misconduct or other improper activities, including noncompliance with regulatory standards and requirements.

We are exposed to the risk that our employees, independent contractors, principal investigators, consultants, vendors, CROs and any partners with which we may collaborate may engage in fraudulent or other illegal activity. Misconduct by these persons could include intentional, reckless or negligent conduct or unauthorized activity that violates: laws or regulations, including those laws requiring the reporting of true, complete and accurate information to the FDA or foreign regulatory authorities; manufacturing standards; federal, state and foreign healthcare fraud and abuse laws and data privacy; or laws that require the true, complete and accurate reporting of financial information or data. In particular, sales, marketing and other business arrangements in the healthcare industry are subject to extensive laws intended to prevent fraud, kickbacks, self-dealing and other abusive practices. These laws may restrict or prohibit a wide range of business activities, including research, manufacturing, distribution, pricing, discounting, marketing and promotion, sales commission, customer incentive programs and other business arrangements. Activities subject to these laws also involve the improper use of information obtained in the course of clinical trials, or illegal misappropriation of drug product, which could result in regulatory sanctions or other actions or lawsuits stemming from a failure to be in compliance with such laws or regulations, and serious harm to our reputation. In addition, federal procurement laws impose substantial penalties for misconduct in connection with government contracts and require certain contractors to maintain a code of business ethics and conduct. If any such actions are instituted against us, and we are not successful in defending ourselves or asserting our rights, those actions could have a significant impact on our business, including the imposition of civil, criminal and administrative penalties, damages, monetary fines, possible exclusion from participation in Medicare, Medicaid and other federal healthcare programs, 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 operating results.

Risks Related to Our Dependence on Third Parties

We expect to rely on third-party CROs and other third parties to conduct and oversee our clinical trials and other aspects of product development. If these third parties do not meet our requirements or otherwise conduct the trials as required, we may not be able to satisfy our contractual obligations or obtain regulatory approval for, or commercialize, our product candidates when expected or at all.

We expect to rely on third-party CROs to conduct and oversee our clinical trials and other aspects of product development. We also rely upon various medical institutions, clinical investigators and contract laboratories to conduct our trials in accordance with our clinical protocols and all applicable regulatory requirements, including the FDA's regulations and GCPs, which are an international standard meant to protect the rights and health of patients and to define the roles of clinical trial sponsors, administrators and monitors, and state regulations governing the handling, storage, security and recordkeeping for drug products. These CROs and other third parties play a significant role in the conduct of these trials and the subsequent collection and analysis of data from the clinical trials. We rely heavily on these parties for the execution of our clinical trials and preclinical studies, and control only certain aspects of their activities. We and our CROs and other third-party contractors are required to comply with GCP and GLP requirements, which are regulations and guidelines enforced by the FDA and comparable foreign regulatory authorities for products in clinical development. Regulatory authorities enforce these GCP and GLP requirements through periodic inspections of trial sponsors, principal investigators and trial sites. If we or any of these third parties fail to comply with applicable GCP and GLP requirements, the clinical data generated in our clinical trials may be deemed unreliable and the FDA or other regulatory authority may require us to perform additional clinical trials before approving our or our partners' marketing applications. We cannot assure you that upon inspection by a given regulatory authority, such regulatory authority will determine that any of our clinical or preclinical trials complies with applicable GCP and GLP requirements. In addition, our clinical trials must generally be conducted with product produced under cGMP regulations. Our failure to comply with these regulations and policies may require us to repeat clinical trials, which would delay the regulatory approval process.

If any of our CROs or clinical trial sites terminate their involvement in one of our clinical trials for any reason, we may not be able to enter into arrangements with alternative CROs or clinical trial sites, or do so on commercially reasonable terms. In addition, if our relationship with clinical trial sites is terminated, we may experience the loss of follow-up information on patients enrolled in our ongoing clinical trials unless we are able to transfer the care of those patients to another qualified clinical trial site. In addition, principal investigators for our clinical trials may serve as scientific advisors or consultants to us from time to time and could receive cash or equity compensation in connection with such services. If these relationships and any related compensation result in perceived or actual conflicts of interest, the integrity of the data generated at the applicable clinical trial site may be questioned by the FDA.

We rely completely on third-party contractors to supply, manufacture and distribute clinical drug supplies for our product candidates, including certain sole-source suppliers and manufacturers, we intend to rely on third parties for commercial supply, manufacturing and distribution if any of our product candidates receive regulatory approval and we expect to rely on third parties for supply, manufacturing and distribution of preclinical, clinical and commercial supplies of any future product candidates. We do not currently have, nor do we plan to acquire, the infrastructure or capability to supply, manufacture or distribute preclinical, clinical or commercial quantities of drug substances or products.

Our ability to develop our product candidates depends and our ability to commercially supply our products will depend, in part, on our ability to successfully obtain the active pharmaceutical ingredients (“ APIs ”) and other substances and materials used in our product candidates from third parties and to have finished products manufactured by third parties in accordance with regulatory requirements and in sufficient quantities for preclinical and clinical testing and commercialization. If we fail to develop and maintain supply relationships with these third parties, we may be unable to continue to develop or commercialize our product candidates.

We do not have direct control over the ability of our contract suppliers and manufacturers to maintain adequate capacity and capabilities to serve our needs, including quality control, quality assurance and qualified personnel. Although we are ultimately responsible for ensuring compliance with regulatory requirements such as cGMPs, we are dependent on our contract suppliers and manufacturers for day-to-day compliance with cGMPs for production of both APIs and finished products. Facilities used by our contract suppliers and manufacturers to produce the APIs and other substances and materials or finished products for commercial sale must pass inspection and be approved by the FDA and other relevant regulatory authorities. Our contract suppliers and manufacturers must comply with cGMP requirements enforced by the FDA through its facilities inspection program and review of submitted technical information. If the safety of any product or product candidate or component is compromised due to a failure to adhere to applicable laws or for other reasons, we may not be able to successfully commercialize or obtain regulatory approval for the affected product or product candidate, and we may be held liable for injuries sustained as a result. Any of these factors could cause a delay or termination of preclinical studies, clinical trials or regulatory submissions or approvals of our product candidates, and could entail higher costs or result in our being unable to effectively commercialize our approved products on a timely basis, or at all.

We also rely and will continue to rely on certain third parties as the sole source of the materials they supply or the finished products they manufacture. In the event an existing supplier fails to supply product on a timely basis or in the requested amount, supplies product that fails to meet regulatory requirements, becomes unavailable through business interruption or financial insolvency or loses its regulatory status as an approved source or if we or our manufacturers are unable to renew current supply agreements when such agreements expire and we do not have a second supplier, we likely would incur added costs and delays in identifying or qualifying replacement manufacturers and materials and there can be no assurance that replacements would be available to us on a timely basis, on acceptable terms or at all. In certain cases we may be required to get regulatory approval to use alternative suppliers, and this process of approval could delay production of our products or development of product candidates indefinitely. We and our manufacturers do not currently maintain inventory of these APIs and other substances and materials. Any interruption in the supply of an active pharmaceutical ingredient (“API”) or other substance or material or in the manufacture of a finished product could have a material adverse effect on our business, financial condition, operating results and prospects.

In addition, these contract manufacturers are engaged with other companies to supply and manufacture materials or products for such companies, which also exposes our suppliers and manufacturers to regulatory risks for the production of such materials and products. As a result, failure to meet the regulatory requirements for the production of those materials and products may also affect the regulatory clearance of a contract supplier’s or manufacturer’s facility. If the FDA or a comparable foreign regulatory agency does not approve these facilities for the supply or manufacture of our product candidates, or if it withdraws its approval in the future, we may need to find alternative supply or manufacturing facilities, which would negatively impact our ability to develop, obtain regulatory approval of or market our product candidates, if approved.

To date, our drug substances and product candidates have been manufactured in small quantities for preclinical studies and early-stage clinical trials. As we prepare for later-stage clinical trials and potential commercialization, we will need to take steps to increase the scale of production of our drug substances and product candidates, which may include transferring production to new third-party suppliers or manufacturers. In order to conduct larger or late-stage scale clinical trials for our product candidates and supply sufficient commercial quantities of the resulting drug product and its components, if that product candidate is approved for sale, our contract manufacturers and suppliers will need to produce our drug substances and product candidates in larger quantities, more cost effectively and, in certain cases, at higher yields than they currently achieve. These third-party contractors may not be able to successfully increase the manufacturing capacity for any of such drug substance and product candidates in a timely or cost-effective manner or at all. Significant scale up of manufacturing may require additional processes, technologies and validation studies, which are costly, may not be successful and which the FDA and foreign regulatory authorities must review and approve. In addition, quality issues may arise during those scale-up activities because of the inherent properties of a product candidate itself or of a product candidate in combination with other components added during the manufacturing and packaging process, or during shipping and storage of the APIs or the finished product. If our third-party contractors are unable to successfully scale up the manufacture of any of our product candidates in sufficient quality and quantity and at commercially reasonable prices, and we are unable to find one or more replacement suppliers or manufacturers capable of production at a substantially equivalent cost in substantially equivalent volumes and quality, and we are unable to successfully transfer the processes on a timely basis, the development of that product candidate and regulatory approval or commercial launch for any resulting products may be delayed, or there may be a shortage in supply, either of which could significantly harm our business, financial condition, operating results and prospects.

We expect to continue to depend on third-party contract suppliers and manufacturers for the foreseeable future. Our supply and manufacturing agreements, if any, do not guarantee that a contract supplier or manufacturer will provide services adequate for our needs. We and our contract suppliers and manufacturers continue to improve production processes, certain aspects of which are complex and unique, and we may encounter difficulties with new or existing processes. While we attempt to build in certain contractual obligations on such third-party suppliers and manufacturers, we may not be able to ensure that such third parties comply with these obligations. Depending on the extent of any difficulties encountered, we could experience an interruption in clinical or commercial supply, with the result that the development, regulatory approval or commercialization of our product candidates may be delayed or interrupted. In addition, third-party suppliers and manufacturers may have the ability to increase the price payable by us for the supply of the APIs and other substances and materials used in our product candidates, in some cases without our consent.

Additionally, any damage to or destruction of our third-party manufacturers' or suppliers' facilities or equipment may significantly impair our ability to have our product candidates manufactured on a timely basis. Furthermore, if a contract manufacturer or supplier becomes financially distressed or insolvent, or discontinues our relationship beyond the term of any existing agreement for any other reason, this could result in substantial management time and expense to identify, qualify and transfer processes to alternative manufacturers or suppliers, and could lead to an interruption in clinical or commercial supply.

Our reliance on contract manufacturers and suppliers further exposes us to the possibility that they, or third parties with access to their facilities, will have access to and may misappropriate our trade secrets or other proprietary information. In addition, the manufacturing facilities of certain of our suppliers are located outside of the United States. This may give rise to difficulties in importing our products or product candidates or their components into the United States or other countries as a result of, among other things, regulatory agency approval requirements or import inspections, incomplete or inaccurate import documentation or defective packaging.

Because we currently rely on a sole supplier to manufacture the active pharmaceutical ingredients of certain of our product candidates, any production problems with our supplier could adversely affect us.

We have relied upon supply agreements with third parties for the manufacture and supply of the bulk active pharmaceutical ingredients used in certain of our product candidates for purposes of preclinical testing and clinical trials. We presently depend upon a single source as the sole manufacturer of our supply of APIs for certain of our product candidates. Although we have identified alternate sources for these supplies, it would be time-consuming and costly to qualify these sources. Since we currently obtain our API from this manufacturer on a purchase-order basis, either we or the supplier may terminate our arrangements, without cause, at any time without notice. If our supplier was to terminate our arrangement or fail to meet our supply needs we might be forced to delay our development.

Manufacturing and supply of the APIs and other substances and materials used in our product candidates and finished drug products is a complex and technically challenging undertaking, and there is potential for failure at many points in the manufacturing, testing, quality assurance and distribution supply chain, as well as the potential for latent defects after products have been manufactured and distributed.

Manufacturing and supply of APIs, other substances and materials and finished drug products is technically challenging. Changes beyond our direct control can impact the quality, volume, price and successful delivery of our product candidates and can impede, delay, limit or prevent the successful development and commercialization of our product candidates. Mistakes and mishandling are not uncommon and can affect successful production and supply. Some of these risks include:

- failure of our manufacturers to follow cGMP requirements or mishandling of product while in production or in preparation for transit;
- inability of our contract suppliers and manufacturers to efficiently and cost-effectively increase and maintain high yields and batch quality, consistency and stability;
- difficulty in establishing optimal drug delivery substances and techniques, production and storage methods and packaging and shipment processes;
- transportation and import/export risk, particularly given the global nature of our supply chain;
- delays in analytical results or failure of analytical techniques that we depend on for quality control and release of product;
- natural disasters, labor disputes, financial distress, lack of raw material supply, issues with facilities and equipment or other forms of disruption to business operations of our contract manufacturers and suppliers; and
- latent defects that may become apparent after product has been released and which may result in recall and destruction of product.

Any of these factors could result in delays or higher costs in connection with our clinical trials, regulatory submissions, required approvals or commercialization of our products, which could harm our business, financial condition, operating results and prospects.

If we are not able to establish and maintain collaborations, we may have to alter our development and commercialization plans.

The development and potential commercialization of our product candidates will require substantial additional cash to fund expenses. In order to fund further development of our product candidates, we may collaborate with pharmaceutical and biotechnology companies for the development and potential commercialization of those product candidates. We face significant competition in seeking appropriate partners. Whether we reach a definitive agreement for a collaboration will depend, among other things, upon our assessment of the partner's resources and experience, the terms and conditions of the proposed collaboration and the proposed partner's evaluation of a number of factors. Those factors may include the design or results of clinical trials; the likelihood of approval by the FDA or other regulatory authorities; the potential market for the subject product candidate; the costs and complexities of manufacturing and delivering such product candidate to patients; the potential of competing products; any uncertainty with respect to our ownership of our intellectual property; and industry and market conditions generally. The partner may also consider alternative product candidates or technologies for similar indications that may be available for collaboration and whether such a collaboration could be more attractive than the one with us for our product candidate. We may also be restricted under future license agreements from entering into agreements on certain terms with potential partners. Collaborations are complex and time-consuming to negotiate and document. In addition, there have been a significant number of business combinations among large pharmaceutical companies that have resulted in a reduced number of potential future partners. Collaborations typically impose detailed obligations on each party. If we were to breach our obligations, we may face substantial consequences, including potential termination of the collaboration, and our rights to our partners' product candidates, in which we have invested substantial time and money, would be lost.

We may not be successful in our efforts to implement collaborations or other alternative arrangements for the development of our product candidates. When we partner with a third party for development and commercialization of a product candidate, we can expect to relinquish to the third party some or all of the control over the future success of that product candidate. Our collaboration partner may not devote sufficient resources to the commercialization of our product candidates or may otherwise fail in their commercialization. The terms of any collaboration or other arrangement that we establish may not be favorable to us, and in any arrangement we may give up material rights related to our product candidates and intellectual property. In addition, any collaboration that we enter into may be unsuccessful in the development and commercialization of our product candidates. In some cases, we may be responsible for continuing preclinical and initial clinical development of a partnered product candidate or research program, and the payment we receive from our collaboration partner may be insufficient to cover the cost of this development.

We may not be able to negotiate collaborations on a timely basis, on acceptable terms or at all. If we are unable to do so, we may have to curtail the development of a product candidate, reduce or delay its development program or one or more of our other development programs, delay its potential commercialization or increase our expenditures and undertake development or commercialization activities at our own expense. If we elect to increase our expenditures to fund development or commercialization activities on our own, we may need to obtain additional capital, which may not be available to us on acceptable terms or at all. If we do not have sufficient funds, we may not be able to further develop our product candidates or bring them to market and generate product revenue.

Risks Related to Our Business and Financial Operations

We will need to further increase the size and complexity of our organization in the future, and we may experience difficulties in executing our growth strategy and managing any growth.

Our management, personnel, systems and facilities currently in place are not adequate to support our business plan and future growth. We will need to further expand our scientific, clinical, managerial, operational, financial and other resources to support our planned research, development and commercialization activities, all of which will require additional capital resources.

Our need to manage our operations, growth and various projects effectively requires that we:

- continue to improve our operational, clinical, financial, management and regulatory compliance controls and reporting systems and procedures;
- attract and retain sufficient numbers of talented employees;
- manage our preclinical and clinical trials effectively;
- manage our third-party supply and manufacturing operations effectively and in a cost-effective manner, while increasing production capabilities for our current product candidates to commercial levels;
- manage our development efforts effectively while carrying out our contractual obligations to partners and other third parties;
- manage our commercialization activities for our product candidates effectively and in a cost-effective manner; and
- establish and maintain relationships with development and commercialization partners.

In addition, historically, we have utilized and continue to utilize the services of part-time outside consultants to perform a number of tasks for us, including tasks related to preclinical and clinical testing. Our growth strategy may also entail expanding our use of consultants to implement these and other tasks going forward. We rely on consultants for certain functions of our business and will need to effectively manage these consultants to ensure that they successfully carry out their contractual obligations and meet expected deadlines. There can be no assurance that we will be able to manage our existing consultants or find other competent outside consultants, as needed, on economically reasonable terms, or at all. If we are not able to effectively manage our growth and expand our organization by hiring new employees and expanding our use of consultants, we might be unable to implement successfully the tasks necessary to execute effectively on our planned research, development and commercialization activities and, accordingly, might not achieve our research, development and commercialization goals.

If we fail to attract and retain management and other key personnel, we may be unable to continue to successfully develop or commercialize our product candidates or otherwise implement our business plan.

Our ability to compete in the highly competitive pharmaceuticals industry depends upon our ability to attract and retain highly qualified managerial, clinical, scientific, medical, sales and marketing and other personnel. We are highly dependent on our management and scientific personnel, including our Chief Executive Officer, Chief Scientific Officer, and our Chief Financial Officer, certain consultants and members of our Board who are well known and respected in our industry. The loss of the services of any of these individuals could impede, delay or prevent the successful development of our product pipeline, completion of our planned clinical trials, commercialization of our product candidates or in-licensing or acquisition of new assets and could negatively impact our ability to successfully implement our business plan. If we lose the services of any of these individuals, we might not be able to find suitable replacements on a timely basis or at all, and our business could be harmed as a result. We do not maintain “key man” insurance policies on the lives of these individuals or the lives of any of our other employees. With the exception of our Chief Executive Officer, Chief Scientific Officer, and our Chief Financial Officer, each of whom is subject to an employment agreement, we employ our executive officers and key personnel on an at-will basis and their employment can be terminated by us or them at any time, for any reason and without notice. In order to retain valuable employees at our company, in addition to salary and cash incentives, we provide 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 stock price that are beyond our control, and may at any time be insufficient to counteract offers from other companies.

We might not be able to attract or retain qualified management and other key personnel in the future due to the intense competition for qualified personnel among biotechnology, pharmaceutical and other businesses, particularly in the Charlottesville, Virginia area where we are headquartered. We could have difficulty attracting experienced personnel to our company and may be required to expend significant financial resources in our employee recruitment and retention efforts. Many of the other pharmaceutical companies with whom we compete for qualified personnel have greater financial and other resources, different risk profiles and longer histories in the industry than we do. They also may provide more diverse opportunities and better chances for career advancement. If we are not able to attract and retain the necessary personnel to accomplish our business objectives, we may experience constraints that will harm our ability to implement our business strategy and achieve our business objectives.

We currently have no sales and marketing personnel or capabilities. If we are unable to establish sales and marketing capabilities on our own or through third parties when we are ready to commercialize our product candidates, we will be unable to successfully commercialize our product candidates, if approved, or generate product revenue.

We currently have no sales and marketing personnel or capabilities. To commercialize our product candidates, if approved, in the United States, Canada, the European Union and other jurisdictions we may seek to enter, we must build our marketing, sales, distribution, managerial and other non-technical capabilities or make arrangements with third parties to perform these services, and we may not be successful in doing so. We as a company have no prior experience in the marketing, sale and distribution of pharmaceutical products and there are significant risks involved in building and managing a sales organization, including our ability to hire, retain and incentivize qualified individuals, generate sufficient sales leads, provide adequate training to sales and marketing personnel and effectively manage a geographically dispersed sales and marketing team. Any failure or delay in the development of our internal sales, marketing and distribution capabilities would adversely impact the commercialization of these products. We may choose to collaborate with additional third parties that have direct sales forces and established distribution systems, either to augment our own sales force and distribution systems or in lieu of our own sales force and distribution systems. If we are unable to enter into such arrangements on acceptable terms or at all, we may not be able to successfully commercialize our product candidates. The inability to successfully commercialize our product candidates, either on our own or through collaborations with one or more third parties, would harm our business, financial condition, operating results and prospects.

If we implement activities to in-license and acquire product candidates and we in-license and acquire commercial-stage products or engage in other strategic transactions, it could impact our liquidity, increase our expenses and present significant distractions to our management.

If we implement a strategy to in-license and acquire product candidates, we may in-license and acquire commercial-stage products or engage in other strategic transactions. Additional potential transactions that we may consider include a variety of different business arrangements, including spin-offs, strategic partnerships, joint ventures, restructurings, divestitures, business combinations and investments. If we issue new equity in connection with a strategic transaction, your ownership interest in us may be diluted. Any such transaction may require us to incur non-recurring or other charges, may increase our near- and long-term expenditures and may pose significant integration challenges or disrupt our management or business, which could adversely affect our operations and financial results. For example, these transactions entail numerous potential operational and financial risks, including:

- exposure to unknown liabilities;
- disruption of our business and diversion of our management’s time and attention in order to develop acquired products, product candidates or technologies;
- incurrence of substantial debt or dilutive issuances of equity securities to pay for acquisitions;
- substantial acquisition and integration costs;
- write-downs of assets or impairment charges;
- increased amortization expenses;
- difficulty and cost in combining the operations and personnel of any acquired businesses with our operations and personnel;
- impairment of relationships with key suppliers, partners or customers of any acquired businesses due to changes in management and ownership; and
- inability to retain our key employees or those of any acquired businesses.

Accordingly, there can be no assurance that we will undertake or successfully complete any transactions of the nature described above, and any transaction that we do complete could harm our business, financial condition, operating results and prospects. We have no current plan, commitment or obligation to enter into any other transaction described above.

Our operating results may fluctuate significantly, which makes our future operating results difficult to predict and could cause our operating results to fall below expectations.

Our near-term operations will be limited primarily to researching and developing our product candidates and undertaking preclinical studies and clinical trials of our product candidates. We have not yet obtained regulatory approvals for any of our product candidates. Consequently, any predictions you make about our future success or viability may not be as accurate as they could be if we had a longer operating history or approved products on the market. From time to time, we may enter into collaboration agreements and license agreements with other companies that include development funding and significant upfront and milestone expenditures and payments, and we expect that amounts earned from or paid pursuant to these agreements will be a significant source of our capital expenditures and an important source of our revenue. Accordingly, our revenue and profitability may depend on development funding and the achievement of development and clinical milestones under potential future collaboration and license agreements and sales of our products, if approved. These upfront and milestone payments may vary significantly from period to period and any such variance could cause a significant fluctuation in our operating results from one period to the next. In addition, we measure compensation cost for stock-based awards made to employees at the grant date of the award, based on the fair value of the award as determined by our Board, and recognize the cost as an expense over the employee's requisite service period. As the variables that we use as a basis for valuing these awards change over time, including our underlying stock price and estimated volatility, the magnitude of the expense that we must recognize may vary significantly. Furthermore, our operating results may fluctuate due to a variety of other factors, many of which are outside of our control and may be difficult to predict, including the following:

- delays in the commencement, enrollment and the timing of clinical testing for our product candidates;
- the timing and success or failure of clinical trials for our product candidates or competing product candidates, or any other change in the competitive landscape of our industry, including consolidation among our competitors or partners;
- any delays in regulatory review and approval of product candidates in clinical development;
- the timing and cost of, and level of investment in, research and development activities relating to our product candidates, which may change from time to time;
- the cost of manufacturing our product candidates, which may vary depending on FDA guidelines and requirements, and the quantity of production;
- our ability to obtain additional funding to develop our product candidates;
- expenditures that we will or may incur to acquire or develop additional product candidates and technologies;
- the level of demand for our product candidates, should they receive approval, which may vary significantly;
- potential side effects of our product candidates that could delay or prevent commercialization or cause an approved drug to be taken off the market;
- the ability of patients or healthcare providers to obtain coverage of or sufficient reimbursement for our product candidates, if approved;
- our dependency on third-party manufacturers to supply or manufacture our product candidates;
- our ability to establish an effective sales, marketing and distribution infrastructure in a timely manner;
- market acceptance of our product candidates, if approved, and our ability to forecast demand for those product candidates;
- our ability to receive approval and commercialize our product candidates outside of the United States;
- our ability to establish and maintain collaborations, licensing or other arrangements;
- our ability and third parties' abilities to protect intellectual property rights;
- costs related to and outcomes of potential litigation or other disputes;
- our ability to adequately support future growth;
- our ability to attract and retain key personnel to manage our business effectively;
- our ability to maintain adequate insurance policies; and

- future accounting pronouncements or changes in our accounting policies.

If we fail to comply with environmental, health and safety laws and regulations, we could become subject to fines or penalties or incur significant costs.

In connection with our research and development activities and our manufacture of materials and product candidates, we are subject to federal, state and local laws, rules, regulations and policies governing the use, generation, manufacture, storage, air emission, effluent discharge, handling and disposal of certain materials, biological specimens and wastes. Although we believe that we have complied with the applicable laws, regulations and policies in all material respects and have not been required to correct any material noncompliance, we may be required to incur significant costs to comply with environmental and health and safety regulations in the future. Current or future laws and regulations may impair our research, development or production efforts. Failure to comply with these laws and regulations also may result in substantial fines, penalties or other sanctions.

Our operating results and liquidity needs could be negatively affected by market fluctuations and economic downturn.

Our operating results and liquidity could be negatively affected by economic conditions generally, both in the United States and elsewhere around the world. Domestic and international equity and debt markets have experienced and may continue to experience heightened volatility and turmoil based on domestic and international economic conditions and concerns. In the event these economic conditions and concerns continue or worsen and the markets continue to remain volatile, our operating results and liquidity could be adversely affected by those factors in many ways, including weakening demand for certain of our product candidates and making it more difficult for us to raise funds if necessary, and our stock price may decline. Additionally, although we plan to market our products primarily in the United States, our partners may have extensive global operations, indirectly exposing us to risk.

Security breaches and other disruptions in our information technology systems could limit our capacity to effectively monitor and control our operations, compromise our or third parties' confidential information or otherwise adversely affect our operating results or business reputation.

Our information technology systems, some of which are managed by third parties, facilitate our ability to monitor and control our operations and adjust to changing market conditions, including processing, transmitting, storing, managing and supporting a variety of business processes, activities and information. Further, as we pursue our growth and business development strategy and pursue new initiatives that improve our operations, we are also expanding and improving our information technologies, resulting in a larger technological presence and corresponding exposure to cybersecurity risk. Any disruption in any of these systems or the failure of any of these systems to operate as expected could, depending on the magnitude of the problem, adversely affect our operating results by limiting our capacity to effectively monitor and control our operations and adjust to changing market conditions.

Additionally, we collect and store sensitive data, including proprietary business information and the proprietary business information of third parties, in data centers and on information technology networks, including cloud-based networks. The secure operation of these information technology networks and the processing and maintenance of this information is critical to our business operations and strategy. Despite security measures and business continuity plans, our information technology networks and infrastructure may be vulnerable to damage, disruptions or shutdowns due to attacks by cyber criminals or breaches due to employee error or malfeasance or other disruptions during the process of upgrading or replacing computer software or hardware, power outages, computer viruses, telecommunication or utility failures, terrorist acts or natural disasters or other catastrophic events. Further, the growing use and rapid evolution of technology, including mobile devices, has heightened the risk of unintentional data breaches or leaks. The occurrence of any of these events could compromise our networks, and the information stored there could be accessed, publicly disclosed, lost or stolen. In addition, as security threats continue to evolve we may need to invest additional resources to protect the security of our systems or to comply with privacy, data security, cybersecurity and data protection laws applicable to our business. The risk of a security breach or disruption, particularly through cyber-attacks or cyber-intrusion, including by computer hackers, criminals, foreign governments, and cyber terrorists, has generally increased as the number, intensity and sophistication of attempted attacks and intrusions from around the world have increased. The loss of clinical trial data from completed or ongoing or planned clinical trials could result in delays in our regulatory approval efforts and significantly increase our costs to recover or reproduce the data.

Any failure to effectively prevent, detect and/or recover from any such access, disclosure or other loss of information, or to comply with any such current or future law related thereto, could result in legal claims or proceedings, liability or regulatory penalties under laws protecting the privacy of personal information, disrupt operations, and damage our reputation, which could adversely affect our business.

Our ability to utilize our net operating loss (“NOL”) carryforwards and other deferred tax assets may be limited.

As of December 31, 2018, the Company had \$45.7 million in federal and state NOL carryforwards available to reduce future taxable income, if any, for income tax purposes. If not utilized, the federal and Virginia NOL carryforwards will begin expiring during the year ending December 31, 2034. Under Section 382 of Internal Revenue Code of 1986, as amended (the “Code”), if a corporation undergoes an “ownership change,” generally defined as a greater than 50% change (by value) in its equity ownership over a three-year period, the corporation’s ability to use its pre-change NOL carryforwards and other pre-change tax attributes (such as research tax credits) to offset its post-change income may be limited. We believe that our reverse merger in January 2016 and other transactions that have occurred, triggered an “ownership change” limitation that significantly limited our ability to utilize our NOL carryforwards. Our 2017 and 2018 financing transactions may have also triggered an ownership change, which could further limit our ability to utilize our NOL carryforwards. We have yet to determine this potential limitation. We may also experience ownership changes in the future as a result of strategic transactions or partnerships, equity offerings and other shifts in our stock ownership. As a result, if we earn net taxable income, our ability to use our pre-change NOL carryforwards and other deferred tax assets to offset U.S. federal taxable income may be subject to limitations, which could potentially result in increased future tax liability to us. In addition, similar limitations may apply at the state level and there may be periods during which the use of NOL carryforwards is suspended or otherwise limited, which could accelerate or permanently increase state taxes owed.

We may be adversely affected by natural disasters and other catastrophic events, and by man-made problems such as terrorism, that could disrupt our business operations and our business continuity and disaster recovery plans may not adequately protect us from a serious disaster.

Our corporate headquarters are located in Charlottesville, Virginia. If a disaster, power outage or other event occurred that prevented us from using all or a significant portion of our headquarters, that damaged critical infrastructure, such as enterprise financial systems, manufacturing resource planning or enterprise quality systems, or that otherwise disrupted operations, it may be difficult or, in certain cases, impossible for us to continue our business for a substantial period of time. Our contract manufacturers’ and suppliers’ facilities are located in multiple locations, where other natural disasters or similar events, such as blizzards, tornadoes, earthquakes, fires, explosions or large-scale accidents or power outages, could severely disrupt our operations and have a material adverse effect on our business, financial condition, operating results and prospects. In addition, acts of terrorism and other geo-political unrest could cause disruptions in our business or the businesses of our partners, manufacturers or the economy as a whole. All of the aforementioned risks may be further increased if we do not implement a disaster recovery plan or our partners’ or manufacturers’ disaster recovery plans prove to be inadequate. To the extent that any of the above should result in delays in the regulatory approval, manufacture, distribution or commercialization of our product candidates, our business, financial condition, operating results and prospects would suffer.

Risks Related to Our Intellectual Property

We may not be able to obtain or enforce patent rights or other intellectual property rights that cover our product candidates and technologies that are of sufficient breadth to prevent third parties from competing against us.

Our success with respect to our product candidates and technologies will depend in part on our ability to obtain and maintain patent protection in both the United States and other countries, to preserve our trade secrets and to prevent third parties from infringing upon our proprietary rights. Our ability to protect any of our product candidates from unauthorized or infringing use by third parties depends in substantial part on our ability to obtain and maintain valid and enforceable patents.

Our patent portfolio includes patents and patent applications in the United States and foreign jurisdictions where we believe there is a market opportunity for our products. The covered technology and the scope of coverage vary from country to country. For those countries where we do not have granted patents, we may not have any ability to prevent the unauthorized use of our technologies. Any patents that we may obtain may be narrow in scope and thus easily circumvented by competitors. Further, in countries where we do not have granted patents, third parties may be able to make, use or sell products identical to or substantially similar to, our product candidates.

The patent application process, also known as patent prosecution, is expensive and time-consuming, and we and our current or future licensors and licensees may not be able to prepare, file and prosecute all necessary or desirable patent applications at a reasonable cost or in a timely manner. It is also possible that we or our current licensors, or any future licensors or licensees, will fail to identify patentable aspects of inventions made in the course of development and commercialization activities before it is too late to obtain patent protection on them. Therefore, these and any of our patents and applications may not be prosecuted and enforced in a manner consistent with the best interests of our business. It is possible that defects of form in the preparation or filing of our patents or patent applications may exist, or may arise in the future, such as with respect to proper priority claims, inventorship, claim scope or patent term adjustments. If our current licensors, or any future licensors or licensees, are not fully cooperative or disagree with us as to the prosecution, maintenance or enforcement of any patent rights, such patent rights could be compromised and we might not be able to prevent third parties from making, using and selling competing products. If there are material defects in the form or preparation of our patents or patent applications, such patents or applications may be invalid and unenforceable. Moreover, our competitors may independently develop equivalent knowledge, methods and know-how. Any of these outcomes could impair our ability to prevent competition from third parties, which may have an adverse impact on our business, financial condition and operating results.

Due to legal standards relating to patentability, validity, enforceability and claim scope of patents covering pharmaceutical inventions, our ability to obtain, maintain and enforce patents is uncertain and involves complex legal and factual questions. Accordingly, rights under any existing patents or any patents we might obtain or license may not cover our product candidates, or may not provide us with sufficient protection for our product candidates to afford a commercial advantage against competitive products or processes, including those from branded and generic pharmaceutical companies. In addition, we cannot guarantee that any patents will issue from any pending or future patent applications owned by or licensed to us. Even if patents have issued or will issue, we cannot guarantee that the claims of these patents are or will be held valid or enforceable by the courts or will provide us with any significant protection against competitive products or otherwise be commercially valuable to us.

Competitors in the fields of oncology have created a substantial amount of prior art, including scientific publications, patents and patent applications. Our ability to obtain and maintain valid and enforceable patents depends on whether the differences between our technology and the prior art allow our technology to be patentable over the prior art. Although we believe that our technology includes certain inventions that are unique and not duplicative of any prior art, we do not have outstanding issued patents covering all of the recent developments in our technology and we are unsure of the patent protection that we will be successful in obtaining, if any. Even if the patents do successfully issue, third parties may design around or challenge the validity, enforceability or scope of such issued patents or any other issued patents we own or license, which may result in such patents being narrowed, invalidated or held unenforceable. If the breadth or strength of protection provided by the patents we hold or pursue with respect to our product candidates is challenged, it could dissuade companies from collaborating with us to develop, or threaten our ability to commercialize, our product candidates.

The laws of some foreign jurisdictions do not provide intellectual property rights to the same extent as in the United States and many companies have encountered significant difficulties in protecting and defending such rights in foreign jurisdictions. If we encounter such difficulties in protecting or are otherwise precluded from effectively protecting our intellectual property in foreign jurisdictions, our business prospects could be substantially harmed. The patent positions of pharmaceutical and biotechnology companies can be highly uncertain and involve complex legal and factual questions for which important legal principles remain unresolved. Changes in either the patent laws or in the interpretations of patent laws in the United States and other countries may diminish the value of our intellectual property. Accordingly, we cannot predict the breadth of claims that may be allowed or enforced in our patents or in third-party patents.

The degree of future protection of our proprietary rights is uncertain. Patent protection may be unavailable or severely limited in some cases and may not adequately protect our rights or permit us to gain or keep our competitive advantage. For example:

- we might not have been the first to invent or the first to file the inventions covered by each of our pending patent applications and issued patents;
- others may independently develop similar or alternative technologies or duplicate any of our technologies;
- the patents of others may have an adverse effect on our business;
- any patents we obtain or our licensors' issued patents may not encompass commercially viable products, may not provide us with any competitive advantages or may be challenged by third parties;
- any patents we obtain or our in-licensed issued patents may not be valid or enforceable; and
- we may not develop additional proprietary technologies that are patentable.

Patents have a limited lifespan. In the United States, the natural expiration of a patent is generally 20 years after it is filed. Various extensions may be available; however the life of a patent, and the protection it affords, is limited. Without patent protection for our product candidates, we may be open to competition from generic versions of our product candidates. Further, the extensive period of time between patent filing and regulatory approval for a product candidate limits the time during which we can market a product candidate under patent protection, which may particularly affect the profitability of our early-stage product candidates.

Proprietary trade secrets and unpatented know-how are also very important to our business. Although we have taken steps to protect our trade secrets and unpatented know-how by entering into confidentiality agreements with third parties, and intellectual property protection agreements with certain employees, consultants and advisors, third parties may still obtain this information or we may be unable to protect our rights. We also have limited control over the protection of trade secrets used by our suppliers, manufacturers and other third parties. There can be no assurance that binding agreements will not be breached, that we would have adequate remedies for any breach or that our trade secrets and unpatented know-how will not otherwise become known or be independently discovered by our competitors. If trade secrets are independently discovered, we would not be able to prevent their use. Enforcing a claim that a third party illegally obtained and is using our trade secrets or unpatented know-how is expensive and time-consuming, and the outcome is unpredictable. In addition, courts outside the United States may be less willing to protect trade secret information.

Changes in patent law could diminish the value of patents in general, thereby impairing our ability to protect our product candidates.

The United States has enacted and is currently implementing wide-ranging patent reform legislation. Further, U.S. Supreme Court rulings have either narrowed the scope of patent protection available in certain circumstances or weakened the rights of patent owners in certain situations. In addition to increasing uncertainty with regard to our ability to obtain patents in the future, this combination of events has created uncertainty with respect to the scope and value of patents, once obtained.

For our U.S. patent applications containing a priority claim after March 16, 2013, there is a greater level of uncertainty in the patent law. In September 2011, the Leahy-Smith America Invents Act, also known as the America Invents Act (“AIA”) was signed into law. The AIA includes a number of significant changes to U.S. patent law, including provisions that affect the way patent applications will be prosecuted and may also affect patent litigation. The USPTO is currently developing regulations and procedures to govern administration of the AIA, and many of the substantive changes to patent law associated with the AIA. It is not clear what other, if any, impact the AIA will have on the operation of our business. Moreover, the AIA and its implementation could increase the uncertainties and costs surrounding the prosecution of our patent applications and the enforcement or defense of our issued patents, all of which could have an adverse effect on our business. An important change introduced by the AIA is that, as of March 16, 2013, the United States transitioned to a “first-to-file” system for deciding which party should be granted a patent when two or more patent applications are filed by different parties claiming the same invention. A third party that files a patent application in the USPTO after that date but before us could therefore be awarded a patent covering an invention of ours even if we had made the invention before it was made by the third party. This will require us to be cognizant going forward of the time from invention to filing of a patent application.

Among some of the other changes introduced by the AIA are changes that limit where a patentee may file a patent infringement suit and providing opportunities for third parties to challenge any issued patent in the USPTO. This applies to all of our U.S. patents, even those issued before March 16, 2013. Because of a lower evidentiary standard in USPTO proceedings compared to the evidentiary standard in United States federal court necessary to invalidate a patent claim, a third party could potentially provide evidence in a USPTO proceeding sufficient for the USPTO to hold a claim invalid even though the same evidence would be insufficient to invalidate the claim if first presented in a district court action. Accordingly, a third party may attempt to use the USPTO procedures to invalidate our patent claims that would not have been invalidated if first challenged by the third party as a defendant in a district court action.

Depending on decisions by the U.S. Congress, the U.S. federal courts, the USPTO or similar authorities in foreign jurisdictions, the laws and regulations governing patents could change in unpredictable ways that may weaken our and our licensors’ ability to obtain new patents or to enforce existing patents we and our licensors or partners may obtain in the future.

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

Filing, prosecuting and defending patents on our product candidates in all countries throughout the world would be prohibitively expensive. The requirements for patentability may differ in certain countries, particularly developing countries. In addition, the laws of some foreign countries do not protect intellectual property rights to the same extent as 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. 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 on infringing activities is inadequate. These products may compete with our products, and our patents or other intellectual property rights may not be effective or sufficient to prevent them from competing.

Many companies have encountered significant problems in protecting and defending intellectual property rights in foreign jurisdictions. The legal systems of certain countries, particularly certain developing countries, do not favor the enforcement of patents and other intellectual property protection, particularly those relating to pharmaceuticals, 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. In addition, certain countries in Europe and certain developing countries have compulsory licensing laws under which a patent owner may be compelled to grant licenses to third parties. In those countries, we may have limited remedies if our patents are infringed or if we are compelled to grant a license to our patents to a third party, which could materially diminish the value of those patents. This could limit our potential revenue opportunities. 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 own or license. Finally, our ability to protect and enforce our intellectual property rights may be adversely affected by unforeseen changes in foreign intellectual property laws.

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 and annuity fees on any issued patent are due to be paid to the USPTO and foreign patent agencies in several stages over the lifetime of the patent. The USPTO 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 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 an adverse effect on our business.

If we are sued for infringing intellectual property rights of third parties, it will be costly and time-consuming, and an unfavorable outcome in that litigation could have a material adverse effect on our business.

Our commercial success depends upon our ability to develop, manufacture, market and sell our product candidates and use our proprietary technologies without infringing the proprietary rights of third parties. We cannot assure you that marketing and selling such candidates and using such technologies will not infringe existing or future patents. Numerous U.S. and foreign issued patents and pending patent applications owned by third parties exist in the fields relating to our product candidates. As the biotechnology and pharmaceutical industries expand and more patents are issued, the risk increases that others may assert that our product candidates, technologies or methods of delivery or use infringe their patent rights. Moreover, it is not always clear to industry participants, including us, which patents cover various drugs, biologics, drug delivery systems or their methods of use, and which of these patents may be valid and enforceable. Thus, because of the large number of patents issued and patent applications filed in our fields, there may be a risk that third parties may allege they have patent rights encompassing our product candidates, technologies or methods.

In addition, there may be issued patents of third parties that are infringed or are alleged to be infringed by our product candidates or proprietary technologies. Because some patent applications in the United States may be maintained in secrecy until the patents are issued, because patent applications in the United States and many foreign jurisdictions are typically not published until eighteen (18) months after filing and because publications in the scientific literature often lag behind actual discoveries, we cannot be certain that others have not filed patent applications for technology covered by our own and in-licensed issued patents or our pending applications. Our competitors may have filed, and may in the future file, patent applications covering our product candidates or technology similar to ours. Any such patent application may have priority over our own and in-licensed patent applications or patents, which could further require us to obtain rights to issued patents covering such technologies. If another party has filed a U.S. patent application on inventions similar to those owned or in-licensed to us, we or, in the case of in-licensed technology, the licensor may have to participate, in the United States, in an interference proceeding to determine priority of invention.

We may be exposed to, or threatened with, future litigation by third parties having patent or other intellectual property rights alleging that our product candidates or proprietary technologies infringe such third parties' intellectual property rights, including litigation resulting from filing under Paragraph IV of the Hatch-Waxman Act. These lawsuits could claim that there are existing patent rights for such drug and this type of litigation can be costly and could adversely affect our operating results and divert the attention of managerial and technical personnel, even if we do not infringe such patents or the patents asserted against us are ultimately established as invalid. There is a risk that a court would decide that we are infringing the third party's patents and would order us to stop the activities covered by the patents. In addition, there is a risk that a court will order us to pay the other party damages for having violated the other party's patents.

There is a substantial amount of litigation involving patent and other intellectual property rights in the biotechnology and pharmaceutical industries generally. To date, no litigation asserting infringement claims has been brought against us. If a third party claims that we infringe its intellectual property rights, we may face a number of issues, including:

- infringement and other intellectual property claims which, regardless of merit, may be expensive and time-consuming to litigate and may divert our management's attention from our core business;
- substantial damages for infringement, which we may have to pay if a court decides that the product or technology at issue infringes or violates the third party's rights, and if the court finds that the infringement was willful, we could be ordered to pay treble damages and the patent owner's attorneys' fees;
- a court prohibiting us from selling or licensing the product or using the technology unless the third party licenses its intellectual property rights to us, which it is not required to do;
- if a license is available from a third party, we may have to pay substantial royalties or upfront fees or grant cross-licenses to intellectual property rights for our products or technologies; and
- redesigning our products or processes so they do not infringe, which may not be possible or may require substantial monetary expenditures and time.

Some of our competitors may be able to sustain the costs of complex patent litigation more effectively than we can because they have substantially greater resources. In addition, any uncertainties resulting from the initiation and continuation of any litigation could harm our ability to raise additional funds or otherwise adversely affect our business, financial condition, operating results and prospects.

Because we may in the future rely on certain third-party licensors and partners, if one of those licensors or partners is sued for infringing a third party's intellectual property rights, our business, financial condition, operating results and prospects could suffer in the same manner as if we were sued directly. In addition to facing litigation risks, we may agree in the future to indemnify certain third-party licensors and partners against claims of infringement caused by our proprietary technologies, and we may enter into cost-sharing agreements with some our licensors and partners that could require us to pay some of the costs of patent litigation brought against those third parties whether or not the alleged infringement is caused by our proprietary technologies. In certain instances, these cost-sharing agreements could also require us to assume greater responsibility for infringement damages than would be assumed just on the basis of our technology.

The occurrence of any of the foregoing could adversely affect our business, financial condition, operating results and prospects.

We may become involved in lawsuits to protect or enforce our patents or other intellectual property which could be expensive and time-consuming.

Competitors may infringe our intellectual property, including our patents. As a result, we may be required to file infringement claims to stop third-party infringement or unauthorized use. This can be expensive, particularly for a company of our size, and time-consuming. In addition, in an infringement proceeding, a court may decide that a patent of ours 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 patent claims do not cover its technology or that the factors necessary to grant an injunction against an infringer are not satisfied. An adverse determination of any litigation or other proceedings could put one or more of our patents at risk of being invalidated, interpreted narrowly or amended such that they do not cover our product candidates. Moreover, such adverse determinations could put our patent applications at risk of not issuing, or issuing with limited and potentially inadequate scope to cover our product candidates or to prevent others from marketing similar products.

Interference, derivation or other proceedings brought at the USPTO may be necessary to determine the priority or patentability of inventions with respect to our patent applications or those of our licensors or potential partners. Litigation or USPTO proceedings brought by us may fail or may be invoked against us by third parties. Even if we are successful, domestic or foreign litigation or USPTO or foreign patent office proceedings may result in substantial costs and distraction to our management. We may not be able, alone or with our licensors or potential partners, to prevent misappropriation of our proprietary rights, particularly in countries where the laws may not protect such rights as fully as in the United States.

Furthermore, because of the substantial amount of discovery required in connection with intellectual property litigation or other proceedings, there is a risk that some of our confidential information could be compromised by disclosure during this type of litigation or other proceedings. In addition, during the course of this kind of litigation or proceedings, there could be public announcements of the results of hearings, motions or other interim proceedings or developments or public access to related documents. If investors perceive these results to be negative, the market price for Common Stock could be significantly harmed.

We may be subject to claims that our employees, consultants or independent contractors have wrongfully used or disclosed to us alleged trade secrets of their former employers or their former or current customers.

As is common in the biotechnology and pharmaceutical industries, certain of our employees were formerly employed by other biotechnology or pharmaceutical companies, including our competitors or potential competitors. Moreover, we engage the services of consultants to assist us in the development of our product candidates, many of whom were previously employed at or may have previously been or are currently providing consulting services to, other biotechnology or pharmaceutical companies, including our competitors or potential competitors. We may be subject to claims that these employees and consultants or we have inadvertently or otherwise used or disclosed trade secrets or other proprietary information of their former employers or their former or current customers. Although we have no knowledge of any such claims being alleged to date, if such claims were to arise, litigation may be necessary to defend against any such claims. Even if we are successful in defending against any such claims, any such litigation could be protracted, expensive, a distraction to our management team, not viewed favorably by investors and other third parties and may potentially result in an unfavorable outcome.

Risks Related to Ownership of Our Common Stock and Other Securities

If we cannot continue to satisfy the NASDAQ Capital Market continued listing standards and other NASDAQ rules, our Common Stock could be delisted, which would harm our business, the trading price of our Common Stock, our ability to raise additional capital and the liquidity of the market for our Common Stock.

Our common stock is currently listed on the Nasdaq Capital Market. To maintain the listing of our common stock on the Nasdaq Capital Market, we are required to meet certain listing requirements, including, among others, either: (i) a minimum closing bid price of \$1.00 per share, a market value of publicly held shares (excluding shares held by our executive officers, directors and 10% or more stockholders) of at least \$1 million and stockholders' equity of at least \$2.5 million; or (ii) a minimum closing bid price of \$1.00 per share, a market value of publicly held shares (excluding shares held by our executive officers, directors and 10% or more stockholders) of at least \$1 million and a total market value of listed securities of at least \$35 million.

There is no assurance that we will continue to meet the minimum closing price requirement and other listing requirements. For example, in March 2018 we received a written notice from the staff (the "Staff") of the Listing Qualifications Department of NASDAQ indicating we were not in compliance with Nasdaq Listing Rule 5550(a)(2) (the "Bid Price Rule") because the bid price for our common stock had closed below \$1.00 per share for the previous 30 consecutive business days. To regain compliance with the Bid Price Rule, in December 2018 we effected a reverse stock split of our Common Stock at a ratio of 1 to 15, and, as of the date of this annual report on Form 10-K, are currently in compliance with the continued listing standards of the NASDAQ Capital Market. However, there is no guarantee we will continue to satisfy the NASDAQ Capital Market continued listing standards.

In the event that our common stock is delisted from Nasdaq and is not eligible for quotation or listing on another market or exchange, trading of our common stock could be conducted only in the over-the-counter market or on an electronic bulletin board established for unlisted securities such as the Pink Sheets or the OTC Bulletin Board. In such event, it could become more difficult to dispose of, or obtain accurate price quotations for, our common stock, and there would likely also be a reduction in our coverage by securities analysts and the news media, which could cause the price of our common stock to decline further.

The trading volume of our Common Stock has historically been low and extremely volatile, which may result in decreased periods of liquidity or large, short-term fluctuations in our stock price.

The number of shares of our Common Stock being traded on a daily basis has historically been low and extremely volatile. The quotation of our Common Stock on the NASDAQ Capital Market does not assure that a meaningful, consistent and liquid trading market currently exists.

Any holder of our Common Stock wishing to sell his, her or its shares may cause a significant fluctuation in the trading price of our Common Stock. In addition, low trading volume of a stock increases the possibility that, despite rules against such activity, the price of the stock may be manipulated by persons acting in their own self-interest. We may not have adequate market makers and market making activity to prevent manipulation in our Common Stock. Such volatility may be the result of broad market and industry factors. In addition to market and industry factors, the price and trading volume for Common Stock may be highly volatile for factors specific to our own operations, many of which are beyond our control, including those described elsewhere in this annual report on Form 10-K and our other public filings.

Future issuances of our Common Stock or securities convertible into our Common Stock may depress the market price of our Common Stock.

We need to raise substantial additional funds to continue our operations, fund additional clinical trials of our product candidates and potentially commercialize our product candidates. We plan to continue to finance our operations with a combination of equity issuances, debt arrangements and a possible partnership or license of development and/or commercialization rights to our product candidates.

Issuances of a substantial number of shares of Common Stock or securities convertible into Common Stock in the public or private market could occur at any time. Any issuance, or the perception in the market that the holders of a large number of shares intend to sell shares, could reduce the market price of Common Stock. If a large number of shares of Common Stock or securities convertible into Common Stock are sold in the public market, the sales could reduce the trading price of Common Stock and impede our ability to raise future capital. In January 2018, we completed a public offering of (i) 1,000,000 shares of Common Stock (as adjusted for the Reverse Stock Split), and (ii) warrants to purchase 1,131,375 shares of our Common Stock (as adjusted for the Reverse Stock Split) (together, the “2018 Public Offering”). In connection therewith, we issued to designees of the underwriter of the 2018 Public Offering warrants to purchase up to 1,000,000 shares of Common Stock (as adjusted for the Reverse Stock Split). As of December 31, 2018, we had warrants outstanding to purchase a total of 2,087,012 shares of our Common Stock. As of March 13, 2019, the exercise price on all of our outstanding warrants exceeded our market price per share of Common Stock, however, if our market price increases above the exercise price on some or all of our outstanding warrants, holders of the warrants may exercise the warrants and sell the underlying Common Stock, depressing our price per share of Common Stock.

Additionally, in connection with our 2018 Public Offering, in January 2018, all of our previously outstanding Series A Convertible Preferred Stock converted to shares of Common Stock, and make-whole and accrued dividends on the Series A Convertible Preferred Stock were paid in shares of Common Stock, with an aggregate of 1,400,462 shares of Common Stock being issued (as adjusted for the Reverse Stock Split). All of such shares are covered by effective registration statements, pursuant to which the holders can sell such shares into the public market.

In addition, pursuant to our 2015 Equity Incentive Plan, as amended, our compensation committee is authorized to grant equity-based incentive awards to our directors, executive officers and other employees and service providers, including officers, employees and service providers of our subsidiaries and affiliates. As of March 13, 2019, the number of shares of our common stock we have reserved for issuance under our 2015 Equity Incentive Plan is 77,193 and future option grants and issuances of common stock under our 2015 Equity Incentive Plan will dilute the percentage ownership of our investors and may adversely affect the market price of our common stock.

If we fail to maintain an effective system of internal control over financial reporting, we may not be able to accurately report our financial results or prevent fraud. As a result, stockholders could lose confidence in our financial and other public reporting, which would harm our business and the trading price of Common Stock.

Effective internal controls over financial reporting are necessary for us to provide reliable financial reports and, together with adequate disclosure controls and procedures, are designed to prevent fraud. Any failure to implement required new or improved controls, or difficulties encountered in their implementation, could cause us to fail to meet our reporting obligations. Ineffective internal controls could also cause investors to lose confidence in our reported financial information, which could have a negative effect on the trading price of Common Stock. In addition, any future testing by us conducted in connection with Section 404 of the Sarbanes-Oxley Act of 2002, as amended (“SOX”), or any required subsequent testing by our independent registered public accounting firm, may reveal deficiencies in our internal controls over financial reporting that are deemed to be material weaknesses or that may require prospective or retroactive changes to our consolidated financial statements or identify other areas for further attention or improvement.

We are required, pursuant to Section 404 of SOX, to furnish a report by management on, among other things, the effectiveness of our internal control over financial reporting as of December 31, 2018. However, our independent registered public accounting firm is not required to attest to the effectiveness of our internal control over financial reporting pursuant to Section 404. Under the supervision and with the participation of our Chief Executive Officer and Chief Financial Officer our management conducted an evaluation of the effectiveness of our internal control over financial reporting based on the framework in Internal Control-Integrated Framework (2013) issued by the Committee of Sponsoring Organizations of the Treadway Commission. Based on that evaluation, our management concluded that our internal control over financial reporting was effective as of December 31, 2018. An independent assessment of the effectiveness of our internal controls could detect problems that our management’s assessment might not. Undetected material weaknesses in our internal controls could lead to financial statement restatements and require us to incur the expense of remediation.

Our disclosure controls and procedures may not prevent or detect all errors or acts of fraud.

We are subject to the periodic reporting requirements of the Exchange Act. Our disclosure controls and procedures are designed to reasonably assure that information required to be disclosed by us in reports we file or submit under the Exchange Act is accumulated and communicated to management, recorded, processed, summarized and reported within the time periods specified in the rules and forms of the SEC. We believe that any disclosure controls and procedures or internal controls and procedures, no matter how well conceived and operated, can provide only reasonable, not absolute, assurance that the objectives of the control system are met.

These inherent limitations include the realities that judgments in decision-making can be faulty, and that breakdowns can occur because of simple error or mistake. Additionally, controls can be circumvented by the individual acts of some persons, by collusion of two or more people or by an unauthorized override of the controls. Accordingly, because of the inherent limitations in our control system, misstatements due to error or fraud may occur and not be detected.

We incur significant costs as a result of our public company status and devote substantial management time to operating as a public company.

As a public company, we incur significant legal, accounting and other expenses to comply with the reporting requirements of the Exchange Act and applicable requirements of SOX and the Dodd-Frank Wall Street Reform and Consumer Protection Act, as well as rules and regulations subsequently implemented by the SEC and NASDAQ, including the establishment and maintenance of effective disclosure and financial controls, changes in corporate governance practices and required filing of annual, quarterly and current reports with respect to our business and operating results. These requirements increase our legal and financial compliance costs and make some activities more time-consuming and costly. In addition, our management and other personnel devote significant time and attention to these public company requirements, which diverts their time attention from operational and other business matters.

Delaware law and provisions in our restated articles of incorporation and restated bylaws could make a merger, tender offer or proxy contest difficult, thereby depressing the trading price of Common Stock.

The anti-takeover provisions under Delaware corporate law may discourage, delay or prevent a change of control by prohibiting us from engaging in a business combination with stockholders owning in excess of 15 percent (15%) of our outstanding voting stock for a period of three years after the person becomes an interested stockholder, even if a change of control would be beneficial to our existing stockholders. In addition, our restated articles of incorporation and restated bylaws contain provisions that may make the acquisition of our company more difficult, including the following:

- provide that only our Board will have the right to fill a vacancy created by the expansion of our Board or the resignation, death or removal of a director, which prevents stockholders from being able to fill vacancies on our Board;
- provide that only our Chairman of the Board, our Chief Executive Officer or a majority of our Board will be authorized to call a special meeting of stockholders;
- authorize the issuance of undesignated preferred stock, the terms of which may be established and shares of which may be issued without stockholder approval, and which may include rights superior to the rights of the holders of Common Stock;
- provide that our Board is expressly authorized to make, alter or repeal our bylaws; and
- establish advance notice requirements for nominations for elections to our Board or for proposing matters that can be acted upon by stockholders at stockholder meetings.

These provisions could also discourage proxy contests and make it more difficult for our stockholders to elect directors of their choosing so as to cause us to take certain corporate actions our stockholders may desire to take.

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

The trading market for common stock will depend in part on the research and reports that securities or industry analysts publish about us or our business. We do not currently have and may never obtain research coverage by securities and industry analysts. If no securities or industry analysts commence coverage of our company, the trading price for common stock would be negatively impacted. If we obtain securities or industry analyst coverage and if one or more of the analysts who covers us downgrades our stock or publishes inaccurate or unfavorable research about our business, our stock price would likely decline. If one or more of these analysts ceases coverage of us or fails to publish reports on us regularly, demand for common stock could decrease, which could cause our stock price and trading volume to decline.

Our directors, executive officers and principal stockholders exert significant influence over us and could impede a change of corporate control.

As of March 13, 2019, our directors, executive officers and holders of more than five percent of common stock, together with their affiliates, beneficially owned, in the aggregate, 6% of our outstanding common stock (See “Security Ownership of Certain Beneficial Owners and Management”). As a result, these stockholders, acting together, would have the ability to exert significant influence on matters submitted to our stockholders for approval, including the election of directors and any merger, consolidation or sale of all or substantially all of our assets. In addition, these stockholders, acting together, would have the ability to significantly influence the management and affairs of our company. Accordingly, this concentration of ownership could harm the market price of common stock by:

- delaying, deferring or preventing a change of control of us;
- impeding a merger, consolidation, takeover or other business combination involving us; or
- discouraging a potential acquiror from making a tender offer or otherwise attempting to obtain control of us.

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

The trading market for Common Stock will depend in part on the research and reports that securities or industry analysts publish about us or our business. We do not currently have and may never obtain research coverage by securities and industry analysts. If no securities or industry analysts commence coverage of our company, the trading price for Common Stock would be negatively impacted. If we obtain securities or industry analyst coverage and if one or more of the analysts who covers us downgrades our stock or publishes inaccurate or unfavorable research about our business, our stock price would likely decline. If one or more of these analysts ceases coverage of us or fails to publish reports on us regularly, demand for Common Stock could decrease, which could cause our stock price and trading volume to decline.

We may be at an increased risk of securities litigation, which is expensive and could divert management attention.

The market price of our Common Stock may be volatile, and in the past companies that have experienced volatility in the market price of their stock have been subject to securities class action litigation. We may be the target of this type of litigation in the future. Securities litigation against us could result in substantial costs and divert our management’s attention from other business concerns, which could seriously harm our business.

We have never paid dividends on our capital stock, and we do not anticipate paying any cash dividends in the foreseeable future.

We have never declared nor paid cash dividends on our capital stock. We currently intend to retain any future earnings, if any, to finance the operation and expansion of our business, and we do not expect to declare or pay any dividends in the foreseeable future. Consequently, stockholders must rely on sales of their Common Stock after price appreciation, which may never occur, as the only way to realize any future gains on their investment.

ITEM 1B. UNRESOLVED STAFF COMMENTS

None.

ITEM 2. PROPERTIES

Our principal executive office is located in a leased facility in Charlottesville, Virginia, where we lease approximately 8,000 square feet of office space for approximately \$10,000 per month.

ITEM 3. LEGAL PROCEEDINGS

From time to time, we are subject to various pending or threatened legal actions and proceedings, including those that arise in the ordinary course of its business, which may include employment matters, breach of contract disputes and stockholder litigation. Such actions and proceedings are subject to many uncertainties and to outcomes that are not predictable with assurance and that may not be known for extended periods of time. We record a liability in our consolidated financial statements for costs related to claims, including future legal costs, settlements and judgments, when we have assessed that a loss is probable and an amount can be reasonably estimated. If the reasonable estimate of a probable loss is a range, we record the most probable estimate of the loss or the minimum amount when no amount within the range is a better estimate than any other amount. We disclose a contingent liability even if the liability is not probable or the amount is not estimable, or both, if there is a reasonable possibility that a material loss may have been incurred. In the opinion of management, as of the date hereof, the amount of liability, if any, with respect to these matters, individually or in the aggregate, will not materially affect our consolidated results of operations, financial position or cash flows.

On August 7, 2014, a complaint was filed in the Superior Court of Los Angeles County, California by Paul Feller, the Company's former Chief Executive Officer under the caption *Paul Feller v. RestorGenex Corporation, Pro Sports & Entertainment, Inc., ProElite, Inc. and Stratus Media Group, GmbH* (Case No. BC553996). The complaint asserts various causes of action, including, among other things, promissory fraud, negligent misrepresentation, breach of contract, breach of employment agreement, breach of the covenant of good faith and fair dealing, violations of the California Labor Code and common counts. The plaintiff is seeking, among other things, compensatory damages in an undetermined amount, punitive damages, accrued interest and an award of attorneys' fees and costs. On December 30, 2014, we filed a petition to compel arbitration and a motion to stay the action. On April 1, 2015, the plaintiff filed a petition in opposition to our petition to compel arbitration and a motion to stay the action. After a hearing for the petition and motion on April 14, 2015, the Court granted our petition to compel arbitration and a motion to stay the action. On January 8, 2016, the plaintiff filed an arbitration demand with the American Arbitration Association. On November 19, 2018 at an Order to Show Cause Re Dismissal Hearing, the Court found sufficient grounds not to dismiss the case, and an arbitration hearing has been scheduled for November 4, 2019. We believe this matter is without merit and we intend to defend the arbitration vigorously. Because this matter is in an early stage, we are unable to predict its outcome and the possible loss or range of loss, if any, associated with its resolution or any potential effect the matter may have on our financial position. Depending on the outcome or resolution of this matter, it could have a material effect on our financial position.

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 Price

Our Common Stock trades publicly on the NASDAQ Capital Market under the symbol “DFFN.”

Number of Record Holders

As of March 13, 2019, there were 383 record holders of our common stock. This does not include beneficial owners of our common stock whose stock is held in nominee or “street name”.

Dividends

To date, we have not declared or paid any cash dividends on our common stock and do not intend to do so in the near future. Our Series A stockholders were entitled to a dividend, payable in shares of common stock, and continued to receive this dividend until the mandatory conversion of all of our outstanding Series A Preferred Stock into shares of our common stock in January 2018.

Securities Authorized for Issuance Under Equity Compensation Plans

For certain information concerning securities authorized for issuance under our equity compensation plan, see Item 12 — Security Ownership of Certain Beneficial Owners and Management and Related Stockholder Matters.

Recent Sales of Unregistered Equity Securities

On October 22, 2018, we issued 4,762 shares of Common Stock (as adjusted for the Reverse Stock Split) to Acorn Management Partners, L.L.C. as consideration for advisory services provided to us, pursuant to Rule 506(b) of the Securities Act. Other than this issuance, during the fourth quarter ended December 31, 2018, we did not issue or sell any equity securities of the Company without registration under the Securities Act.

Issuer Purchases of Equity Securities

During the fourth quarter ended December 31, 2018, we did not purchase any shares of our common stock or other Diffusion equity securities.

Our Board of Directors has not authorized any repurchase plan or program for the purchase of shares of our common stock or other securities on the open market or otherwise.

ITEM 6. SELECTED FINANCIAL DATA

Item 6 is not applicable to us as a smaller reporting company and has been omitted.

ITEM 7. MANAGEMENT'S DISCUSSION AND ANALYSIS OF FINANCIAL CONDITION AND RESULTS OF OPERATIONS

Introduction

This Management's Discussion and Analysis provides material historical and prospective disclosures intended to enable investors and other users to assess our financial condition and results of operations. Statements that are not historical are forward-looking and involve risks and uncertainties discussed under the headings " *Part I. Item 1. Business—Cautionary Note Regarding Forward-Looking Statements* " and " *Part I. Item 1A. Risk Factors* " of this report. The following discussion of our results of operations and financial condition should be read in conjunction with our financial statements and the related notes thereto included elsewhere in this report. These risks could cause our actual results to differ materially from any future performance suggested below.

Business Overview

We are a clinical stage biotechnology company developing new treatments for life threatening conditions by improving the body's ability to bring oxygen to the areas where it is needed most. We are developing our lead product candidate, transcrocetin sodium, also known as trans sodium crocetinate ("TSC"), for use in those life threatening conditions in which cellular oxygen deprivation ("hypoxia") is the basis for significant unmet medical needs. TSC is designed to safely and selectively target and re-oxygenate the micro-environment of hypoxic cells, and potentially be used in many indications, including oncology and cardiovascular/stroke. In cancer, TSC re-oxygenates treatment-resistant cancerous tissue, making the cancer cells up to three times more susceptible to the therapeutic effects of standard-of-care radiation therapy and chemotherapy. In stroke, TSC helps promote the diffusion of oxygen into those brain cells in which oxygen-deprivation causes neuronal death resulting in patient mortality or morbidity.

A range of tissue types, including both cancerous and normal cells, has been shown to be safely re-oxygenated in our preclinical and clinical studies using TSC's novel mechanism of action. In oncology, we believe TSC's therapeutic potential is not limited to one specific tumor type, thereby making it potentially useful to improve standard-of-care treatments in many life-threatening cancers. Given TSC's safety profile and animal data, we could, with appropriate funding, move directly into Phase 2 studies in many such cancers. Likewise, we believe TSC's ability to re-oxygenate normal tissue that has become oxygen-deprived provides opportunities for new therapeutic approaches to conditions ranging from stroke and emergency medicine to cardiovascular indications. The successful completion of trials for TSC or any other potential product candidate in these or any other indication are dependent upon our ability to further raise necessary capital.

Our most advanced program targets TSC against treatment-resistant brain cancer. A Phase 2 clinical program, completed in the second quarter of 2015, evaluated 59 patients with newly diagnosed glioblastoma multiforme ("GBM"), a particularly deadly form of primary brain cancer. This open label, historically controlled study demonstrated a favorable safety and efficacy profile for TSC when combined with GBM's standard of care, including a 37% improvement in overall survival over the control group at two years. A particularly strong efficacy signal was seen in the inoperable patients, where survival of TSC-treated patients at two years was increased by almost four-fold over the controls. In December 2017, we initiated the IN vestigation of TSC Against Cancerous Tumors (INTACT) Phase 3 trial in the newly diagnosed inoperable GBM patient population. Patient enrollment began in January 2018. The trial will enroll 236 patients in total, with 118 in the treatment arm and 118 in the control arm. The trial is beginning with an 8 patient safety run-in which the Company expects to be finished in the second quarter of 2019.

Other cancerous tumor targets upon which the Company's technology is focused include pancreatic cancer and brain metastasis, for which an FDA Orphan Designation has been granted to TSC. We believe that TSC programs for such cancers are Phase 2 ready, as safety profiles have been demonstrated in other oncology programs, protocols have been written, FDA interaction has taken place, and key opinion leaders have been engaged. Further research and development of TSC as a potential treatment for these indications is largely dependent on the necessary financial resources becoming available.

We believe that TSC has potential application in other indications involving hypoxia, notably stroke and emergency medicine, as well as cardiovascular and neurodegenerative diseases. A Phase 2 trial program in cooperation with UCLA and the University of Virginia to test TSC in the treatment of acute stroke has received approval for enrollment by the FDA, with the first enrolled patient expected in Q2 2019. This trial, which will feature in-ambulance dosing of TSC, is named the Pre Hospital Acute Stroke Therapy - TSC (PHAST - TSC) and is expected to enroll 160 patients, with 80 in the treatment arm and 80 in the control arm. We believe in-ambulance dosing of TSC could significantly cut the time in which the stroke-related oxygen deprivation to brain cells goes untreated, potentially leading to a better outcome for stroke victims treated in this manner. In the last quarter of 2018, we received FDA permission to begin patient enrollment in the PHAST - TSC Phase 2 trial and expect to begin enrollment so in second quarter 2019, following completion of institutional review board and contracting activities.

In addition to the TSC programs, we are exploring alternatives regarding how best to capitalize upon our product candidate RES-529, which may include possible out-licensing and other options. RES-529 is a novel PI3K/Akt/mTOR pathway inhibitor which has completed two Phase 1 clinical trials for age-related macular degeneration and was in preclinical development in oncology, specifically GBM. RES-529 has shown activity in both in vitro and in vivo glioblastoma animal models and has been demonstrated to be orally bioavailable and capable of crossing the blood brain barrier.

Critical Accounting Policies

Certain of our critical accounting estimates require the application of significant judgment by management in selecting the appropriate assumptions in determining the estimate. By their nature, these judgments are subject to an inherent degree of uncertainty. We develop these judgments based on our historical experience, terms of existing contracts, our observance of trends in the industry and information available from other outside sources, as appropriate. Actual results may differ from these judgments under different assumptions or conditions. Different, reasonable estimates could have been used for the current period. Additionally, changes in accounting estimates are reasonably likely to occur from period to period. Both of these factors could have a material impact on the presentation of our financial condition, changes in financial condition or results of operations. We believe the following accounting estimates are the most critical to aid in fully understanding and evaluating our financial statements as they require our most subjective or complex judgments:

Goodwill

Goodwill is the excess of the cost of an acquired entity over the net amounts assigned to tangible and intangible assets acquired and liabilities assumed. We apply Accounting Standards Codification (ASC) 350 “*Goodwill and Other Intangible Assets*,” which requires testing goodwill for impairment on an annual basis. We assess goodwill for impairment as part of our annual reporting process on October 1 of each year, or more frequently if triggering events indicate a possible impairment. We evaluate goodwill on a consolidated basis as we are organized as a single reporting unit. We consider certain triggering events when evaluating whether an interim goodwill impairment analysis is warranted. Among these would be a significant long-term decrease in our market capitalization. We recognized a non-cash goodwill impairment charge of \$6.9 million during the year ended December 31, 2018.

Intangible Assets

Our sole intangible asset as of December 31, 2018 consists of an in-process research and development (“IPR&D”) intangible asset acquired in 2016. The fair value of the IPR&D asset was determined as of the acquisition date using the cost approach, which establishes a value based on the cost of reproducing or replacing the asset, often referred to as current replacement cost. The cost approach was chosen as we were not able to estimate an income stream attributable to the IPR&D asset given the fact that the related products have only completed limited preclinical and clinical trials and the timeline to commercial viability, if the FDA approval process is successful, is somewhat uncertain and would take a number of years, and the costs would be significant. As the development efforts for our RES-529 IPR&D asset continues, based on the facts and circumstances at the time of a future valuation for the purposes of assessing impairment, it is possible that the value for RES-529 could be substantially reduced or eliminated, which could result in a maximum pretax charge to operations equal to the current carrying value of our intangible asset of \$8.6 million as of December 31, 2018. We tested the IPR&D intangible asset for impairment on October 1, which is our annual impairment testing date. We consider certain triggering events when evaluating whether an interim IPR&D impairment analysis is warranted. There was no impairment to our IPR&D asset during the years ended December 31, 2018 and 2017.

Financial Summary

At December 31, 2018, we had cash and cash equivalents balances of \$8.0 million. We have incurred operating losses since inception, have not generated any product sales revenue and have not achieved profitable operations. We incurred a net loss of \$18.4 million and \$1.4 million for the years ended December 31, 2018 and 2017, respectively. Our accumulated deficit as of December 31, 2018, was \$79.9 million, and we expect to continue to incur substantial losses in future periods. We anticipate that our operating expenses will increase substantially as we continue to advance our lead, clinical-stage product candidate, TSC. We anticipate that our expenses will substantially increase as we:

- continue our Phase III clinical trial for TSC in GBM and begin our Phase 2 clinical trial for TSC in stroke;
- continue the research, development and scale-up manufacturing capabilities to optimize products and dose forms for which we may obtain regulatory approval;
- conduct other preclinical and clinical studies to support the filing of a NDA for TSC with the FDA;
- maintain, expand and protect our global intellectual property portfolio;
- hire additional clinical, manufacturing, and scientific personnel; and
- add, acquire or develop operational, financial and management information systems and personnel, including personnel to support our drug development and potential future commercialization efforts.

We intend to use our existing cash and cash equivalents for working capital and to fund the research and development of TSC. We expect that our existing cash as of December 31, 2018, will enable us to fund our operating expenses and capital expenditure requirements (including our clinical trials) into July 2019.

Financial Operations Overview

Revenues

We have not yet generated any revenue from product sales. We do not expect to generate revenue from product sales for the foreseeable future.

Research and Development Expense

Research and development costs include, but are not limited to, third-party contract research arrangements, employee-related expenses, including salaries, benefits, stock-based compensation and travel expense reimbursement. Research and development activities are central to our business model. Product candidates in later stages of clinical development generally have higher development costs than those in earlier stages of clinical development, primarily due to the increased size and duration of later-stage clinical trials. As we advance our product candidates, we expect the amount of research and development costs will continue to increase for the foreseeable future. Research and development costs are charged to expense as incurred.

General and Administrative Expense

General and administrative expense consists principally of salaries and related costs for executive and other personnel, including stock-based compensation, expenses associated with investment bank and other financial advisory services, and travel expenses. Other general and administrative expenses include professional fees that were incurred in connection with operating as a public company, facility-related costs, communication expenses and professional fees for legal, patent prosecution and maintenance, and consulting and accounting services.

Goodwill Impairment Expense

Goodwill impairment expense relates to a non-cash impairment charge recognized as a write-down of the Company's goodwill due to the Company's carrying value of equity exceeding its fair value throughout the second half of 2018.

Interest (Income) Expense, Net

Interest (income) expense, net consisted principally of the interest expense recorded in connection with our previously outstanding convertible debt instruments offset by the interest earned from our cash and cash equivalents and our certificate of deposit.

Change in Fair Value of Warrant Liabilities, Warrant Related Expenses, and Other Financing Expenses

In connection with our private placement in March 2017, we recorded warrant expense associated with the change in fair value of the common stock warrants from issuance, the excess fair value of the common stock warrants over the gross cash proceeds from our private placement of Series A convertible preferred stock, and placement agent commissions and other offering costs. Until the reclassification of our common stock warrants into stockholders' equity in November 2017 in connection with the amendment of our certificate of incorporation, the warrants were liability classified and remeasured at each reporting period with changes in fair value recorded through earnings on our consolidated statement of operations.

Income Tax Benefit

Since inception, we had incurred net losses and until 2018, we had not recorded any U.S. federal or state income tax benefits for the losses as they had been offset by valuation allowances. As a result of the change in net operating loss carryforward period associated with the Tax Cuts and Jobs Act ("the 2017 Tax Act"), we recognize income tax benefit to reflect the adjustment allowed by the 2017 Tax Act to utilize indefinite deferred tax liabilities as a source of income against indefinite lived portions of our deferred tax assets. For the year ended December 31, 2017, we recognized an income tax benefit for the revaluation of our deferred tax liability as a result of the Tax Cuts and Jobs Act, which reduced our corporate tax rate to 21%. See Note 12 to our consolidated financial statements included in "Item 8. Financial Statements and Supplementary Data" below for further details.

Results of Operations for Year Ended December 31, 2018 Compared to Year Ended December 31, 2017

The following table sets forth our results of operations for the years ended December 31, 2018 and 2017:

	Year ended December 31,		Change
	2018	2017	
Operating expenses:			
Research and development	\$ 5,751,940	\$ 5,088,621	\$ 663,319
General and administrative	6,167,177	6,191,845	(24,668)
Goodwill impairment	6,929,258	—	6,929,258
Depreciation	110,371	67,981	42,390
Loss from operations	18,958,746	11,348,447	7,610,299
Interest (income) expense, net	(151,647)	48,006	(199,653)
Change in fair value of warrant liability	—	(22,072,322)	22,072,322
Warrant related expenses	—	10,225,846	(10,225,846)
Other financing expenses	—	2,870,226	(2,870,226)
Loss from operations before income tax benefit	(18,807,099)	(2,420,203)	(16,386,896)
Income tax benefit	(437,289)	(1,055,685)	618,396
Net loss	<u>\$ (18,369,810)</u>	<u>\$ (1,364,518)</u>	<u>\$ (17,005,292)</u>

Research and development expenses were \$5.8 million during the year ended December 31, 2018 compared to \$5.1 million during the year ended December 31, 2017. This increase in research and development expense was mainly attributable to a \$1.7 million increase in expense related to our Phase 3 GBM trial and an increase in salary and wages expense of \$0.2 million, offset by a decrease in manufacturing and other costs of \$1.2 million.

General and administrative expenses were \$6.2 million during the year ended December 31, 2018 compared to \$6.2 million during the year ended December 31, 2017. Although overall general and administrative expenses were flat, salaries and wages expense increased by \$0.6 million, which was offset by a decrease in professional fees of \$0.6 million.

We recognized a non-cash goodwill impairment charge of \$6.9 million during the year ended December 31, 2018 as a result of a sustained decrease in our market capitalization during the second half of 2018. There was no such charge during the year ended December 31, 2017.

The change in interest (income) expense, net for the year ended December 31, 2018 compared to the year ended December 31, 2017 was primarily attributable to having a larger cash and cash equivalents balance earning more interest during the year ended December 31, 2018 compared to the year ended December 31, 2017. During the year ended December 31, 2017, we had a higher debt principal balance with a higher interest rate outstanding compared to having a smaller debt principal balance outstanding during 2018.

In connection with the private placement of our Series A convertible preferred stock and common stock warrants, we determined the warrants to be classified as liabilities and subject to remeasurement at each reporting period, until November 1, 2017 (See Note 19 of the notes to our audited consolidated financial statements under Item 8). As a result of the liability classification, during 2017, we recorded a \$22.1 million non-cash gain for the change in fair value of our common stock warrant liabilities which was primarily attributable to the decrease in the market price for our common stock. We also recognized \$10.2 million in excess fair value of the common stock warrants over the gross proceeds from our private placement and \$2.9 million in placement agent commissions and other offering costs.

As a result of the change in net operating loss carryforward period associated with the 2017 Tax Act, we recognized an income tax benefit of \$0.4 million during the year ended December 31, 2018 to reflect the utilization of indefinite deferred tax liabilities as a source of income against indefinite lived portions of the our deferred tax assets. For the year ended December 31, 2017, we recognized an income tax benefit of \$1.1 million for the revaluation of our deferred tax liability as a result of the 2017 Tax Act, which reduced our corporate tax rate to 21%.

Liquidity and Capital Resources

Working Capital

The following table summarizes our working capital as of December 31, 2018 and 2017:

	December 31,	
	2018	2017
Cash and cash equivalents	\$ 7,991,172	\$ 8,896,468
Prepaid expenses, deposits and other assets	923,059	769,946
Total current liabilities	804,044	2,690,807
Working capital	<u>\$ 8,110,187</u>	<u>\$ 6,975,607</u>

We expect to continue to incur net losses for the foreseeable future. We intend to use our existing cash and cash equivalents for working capital and to fund the research and development of our product candidates.

Cash Flows

The following table sets forth our cash flows for the years ended December 31, 2018 and 2017:

	December 31,	
	2018	2017
Net cash (used in) provided by:		
Operating activities	\$ (10,772,816)	\$ (12,332,355)
Investing activities	—	(447,823)
Financing activities	9,867,520	20,123,794
Net (decrease) increase in cash and cash equivalents	<u>\$ (905,296)</u>	<u>\$ 7,343,616</u>

Operating Activities

Net cash used in operating activities of \$10.8 million during the year ended December 31, 2018 was primarily attributable to our net loss of \$18.4 million, a \$0.4 million change in deferred income taxes, and our net change in operating assets and liabilities of \$0.3 million. This amount was offset by the recognition of a \$6.9 million non-cash impairment charge to goodwill and \$1.4 million in other non-cash charges, which were made up of stock-based compensation, common stock issued for advisory services and depreciation.

Net cash used in operating activities of \$12.3 million during the year ended December 31, 2017 was primarily attributable to our net loss of \$1.4 million, a \$9.0 million net non-cash gain related to warrants and other financing expenses, a \$1.1 million change in our deferred tax liability due to the change in tax rate, and our net change in operating assets and liabilities of \$2.3 million. The net change in our operating assets and liabilities is primarily attributable to the increase in our prepaid assets related to clinical trial activities and an increase in accrued expenses. This amount was offset by \$1.4 million in non-cash charges, which was made up of stock-based compensation, common stock issued for advisory services, depreciation and non-cash interest expense.

Investing Activities

Net cash used in investing activities was \$0.4 million during the year ended December 31, 2017. We purchased, and had mature, a certificate of deposit in the amount of \$10.0 million and had approximately \$0.4 million in fixed asset purchases, mainly related to the build out of our new headquarters. We had no such activity in 2018.

Financing Activities

Net cash provided by financing activities was \$9.9 million during the during the year ended December 31, 2018, which was attributable to the \$10.8 million in proceeds received upon the sale of our Common Stock offset by approximately \$0.4 million in payments for offering costs. During the year ended December 31, 2018, we also repaid the outstanding principal balance of our Series B convertible notes in the amount of approximately \$0.6 million.

Net cash provided by financing activities was \$20.1 million during the during the year ended December 31, 2017, which was attributable to the \$22.1 million in proceeds received upon the closing of our private placement of our Series A preferred stock in March 2017 offset by approximately \$0.1 million in payments for offering costs. This amount was further offset by the repayment of convertible debt in the amount of \$1.9 million.

Reverse Stock Split

On December 13, 2018, we filed a Certificate of Amendment to our Certificate of Incorporation with the Secretary of State of the State of Delaware to effect a 1-to-15 reverse stock split (the “Reverse Stock Split”) of our common stock. No fractional shares were issued in connection with the Reverse Stock Split. Stockholders who otherwise would have been entitled to receive fractional shares of our common stock had their holdings rounded up to the next whole share. Proportional adjustments were made to our outstanding warrants, stock options and other equity securities and to the our 2015 Equity Incentive Plan, as amended, to reflect the Reverse Stock Split, in each case, in accordance with the terms thereof. Unless the context otherwise requires, all share and per share amounts in this annual report on Form 10-K have been adjusted to reflect the Reverse Stock Split.

Capital Requirements

We expect to continue to incur substantial expenses and generate significant operating losses as we continue to pursue our business strategy of developing our lead product candidate, TSC, for use in the treatment of GBM, stroke and other hypoxia related indications. Our operations have consumed substantial amounts of cash since inception. We expect to continue to spend substantial amounts of cash to advance the clinical development of our product candidates and to commercialize any product candidates for which we receive regulatory approval. At the current time, the bulk of our cash resources for clinical development is dedicated to the Phase 3 trial for TSC in inoperable GBM and the Phase 2 trial for TSC in acute stroke. While we believe we have adequate cash resources to continue operations into July 2019, we will need to raise additional funds in order to complete these trials. We do not expect to commence any clinical trials beyond these trials unless we are able to raise additional capital, enter into a strategic partnership, or make alternative financing arrangements for any such trials. To date, we have funded our ongoing business operations and short-term liquidity needs, primarily through the sale and issuance of preferred stock, common stock and convertible debt. We expect to continue this practice for the foreseeable future, however, we may enter into strategic partnerships or transactions in order to fund our ongoing capital requirements.

As of December 31, 2018, we did not have credit facilities under which we could borrow funds or any other sources of committed capital. We will seek to raise additional funds through various sources, such as equity and debt financings, or through strategic collaborations or licensing agreements. We can give no assurances that we will be able to secure additional sources of funds to support our operations, or if such funds are available to us, that such additional financing will be sufficient to meet our needs or be on terms acceptable to us. This risk may increase if economic and market conditions deteriorate. If we are unable to obtain additional financing when needed, we may need to terminate, significantly modify or delay the development of our product candidates and our operations, or we may need to obtain funds through collaborators that may require us to relinquish rights to our technologies or product candidates that we might otherwise seek to develop or commercialize independently. If we are unable to raise any additional capital in the near-term and/or we cannot significantly reduce our expenses and are forced to terminate our operations, investors may experience a complete loss of their investment.

To the extent that we raise additional capital through the sale of our common stock, the interests of our current stockholders may be diluted. If we issue additional preferred stock or convertible debt securities, it could affect the rights of our common stockholders or reduce the value of our common stock or any outstanding classes of preferred stock. In particular, specific rights granted to future holders of preferred stock or convertible debt securities may include voting rights, preferences as to dividends and liquidation, conversion and redemption rights, sinking fund provisions, and restrictions on our ability to merge with or sell our assets to a third party. Debt financing, if available, may involve agreements that include covenants limiting or restricting our ability to take specific actions, such as incurring additional debt, making capital expenditures or declaring dividends.

Contractual Obligations

As of December 31, 2018, we had the following contractual commitments:

Contractual Obligations	Payments due by period				
	Total	Less than 1 year	1-3 years	3-5 years	More than 5 years
Operating lease ⁽¹⁾	\$ 389,127	\$ 114,409	\$ 274,718	\$ —	\$ —
Total	\$ —	\$ —	\$ —	\$ —	\$ —

⁽¹⁾ Operating lease obligations reflect our obligation to make payments in connection with our corporate headquarters in Charlottesville, Virginia.

Off-Balance Sheet Arrangements

We do not have any off-balance sheet arrangements, as defined by the rules and regulations of the SEC that have or are reasonably likely to have a material effect on our financial condition, changes in financial condition, revenue or expenses, results of operations, liquidity, capital expenditures or capital resources. As a result, we are not materially exposed to any financing, liquidity, market or credit risk that could arise if we had engaged in these arrangements.

Recently Issued Accounting Pronouncements

Recently issued accounting pronouncements are addressed in Note 3 in the Notes to Consolidated Financial Statements included in Item 8 hereto.

ITEM 7A. QUANTITATIVE AND QUALITATIVE DISCLOSURE ABOUT MARKET RISK

Item 7A is not applicable to us as a smaller reporting company and has been omitted.

ITEM 8. FINANCIAL STATEMENTS AND SUPPLEMENTARY DATA

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Report of Independent Registered Public Accounting Firm

To the Stockholders and Board of Directors
Diffusion Pharmaceuticals Inc.:

Opinion on the Consolidated Financial Statements

We have audited the accompanying consolidated balance sheets of Diffusion Pharmaceuticals Inc. and subsidiaries (the Company) as of December 31, 2018 and 2017, the related consolidated statements of operations, stockholders' equity, and cash flows for the years then ended, and the related notes (collectively, the consolidated financial statements). In our opinion, the consolidated financial statements present fairly, in all material respects, the financial position of the Company as of December 31, 2018 and 2017, and the results of their operations and their cash flows for the years then ended, in conformity with U.S. generally accepted accounting principles.

Going Concern

The accompanying consolidated financial statements have been prepared assuming that the Company will continue as a going concern. As discussed in Note 2 to the consolidated financial statements, the Company has suffered recurring losses from operations, has limited resources available to fund current research and development activities, and will require substantial additional financing to continue to fund its research and development activities that raise substantial doubt about its ability to continue as a going concern. Management's plans in regard to these matters are also described in Note 2. The consolidated financial statements do not include any adjustments that might result from the outcome of this uncertainty.

Basis for Opinion

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

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

Our audits included performing procedures to assess the risks of material misstatement of the 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. We believe that our audits provide a reasonable basis for our opinion.

/s/ KPMG LLP

We have served as the Company's auditor since 2015.

McLean, Virginia
March 19, 2019

DIFFUSION PHARMACEUTICALS INC.

CONSOLIDATED BALANCE SHEETS

	December 31,	
	2018	2017
Assets		
Current assets:		
Cash and cash equivalents	\$ 7,991,172	\$ 8,896,468
Prepaid expenses, deposits and other current assets	923,059	769,946
Total current assets	8,914,231	9,666,414
Property and equipment, net	350,281	460,652
Intangible asset	8,639,000	8,639,000
Goodwill	—	6,929,258
Other assets	298,480	450,491
Total assets	\$ 18,201,992	\$ 26,145,815
Liabilities, Convertible Preferred Stock and Stockholders' Equity		
Current liabilities:		
Current portion of convertible debt	\$ —	\$ 550,000
Accounts payable	198,818	511,956
Accrued expenses and other current liabilities	605,226	1,628,851
Total current liabilities	804,044	2,690,807
Deferred income taxes	1,786,389	2,223,678
Other liabilities	—	1,386
Total liabilities	2,590,433	4,915,871
Commitments and Contingencies (Note 8)		
Convertible preferred stock, \$0.001 par value:	—	—
Series A - No shares authorized, issued or outstanding at December 31, 2018, 13,750,000 shares authorized, 12,376,329 shares issued and 8,306,278 shares outstanding at December 31, 2017	—	—
Stockholders' Equity:		
Common stock, \$0.001 par value: 1,000,000,000 shares authorized; 3,376,230 and 967,976 shares issued and outstanding at December 31, 2018 and 2017, respectively	3,377	968
Additional paid-in capital	95,532,881	82,783,865
Accumulated deficit	(79,924,699)	(61,554,889)
Total stockholders' equity	15,611,559	21,229,944
Total liabilities, convertible preferred stock and stockholders' equity	\$ 18,201,992	\$ 26,145,815

See accompanying notes to consolidated financial statements.

DIFFUSION PHARMACEUTICALS INC.

CONSOLIDATED STATEMENTS OF OPERATIONS

	Year Ended December 31,	
	2018	2017
Operating expenses:		
Research and development	\$ 5,751,940	\$ 5,088,621
General and administrative	6,167,177	6,191,845
Goodwill impairment	6,929,258	—
Depreciation	110,371	67,981
Loss from operations	18,958,746	11,348,447
Other expense (income):		
Interest (income) expense, net	(151,647)	48,006
Change in fair value of warrant liability	—	(22,072,322)
Warrant related expenses	—	10,225,846
Other financing expenses	—	2,870,226
Loss from operations before income tax benefit	(18,807,099)	(2,420,203)
Income tax benefit	(437,289)	(1,055,685)
Net loss	\$ (18,369,810)	\$ (1,364,518)
Accretion of Series A cumulative preferred dividends	(85,993)	(1,252,394)
Deemed dividend related to the make-whole provision for the conversion of Series A convertible preferred stock into common stock	(8,167,895)	—
Net loss attributable to common stockholders	\$ (26,623,698)	\$ (2,616,912)
Per share information:		
Net loss per share of common stock, basic	\$ (8.21)	\$ (3.16)
Net loss per share of common stock, diluted	\$ (8.21)	\$ (29.11)
Weighted average shares outstanding, basic	3,242,301	827,575
Weighted average shares outstanding, diluted	3,242,301	848,090

See accompanying notes to consolidated financial statements.

DIFFUSION PHARMACEUTICALS INC.

CONSOLIDATED STATEMENTS OF CHANGES IN STOCKHOLDERS' EQUITY

	Convertible Preferred Stock		Stockholders' Equity				
	Series A		Common Stock		Additional Paid-in Capital	Accumulated Deficit	Total Stockholders' Equity
	Shares	Amount	Shares	Amount			
Balance at January 1, 2017	—	—	689,709	690	69,373,231	(60,189,237)	9,184,684
Cumulative effect of change in accounting principle ^(a)	—	—	—	—	1,134	(1,134)	—
Sale of Series A convertible preferred stock and common stock warrants	12,376,329	—	—	—	—	—	—
Reclassification of the fair market value of the Series A warrants	—	—	—	—	13,153,524	—	13,153,524
Common stock issued for advisory services	—	—	1,174	1	49,999	—	50,000
Series A cumulative preferred dividend	—	—	—	—	(1,252,394)	—	(1,252,394)
Reclassification of accrued dividends upon conversion of Series A	—	—	5,756	6	190,074	—	190,080
Conversion of Series A convertible preferred stock to common stock	(4,070,051)	—	271,337	271	(271)	—	—
Beneficial conversion feature for accrued interest of convertible debt	—	—	—	—	28,017	—	28,017
Stock-based compensation expense	—	—	—	—	1,240,551	—	1,240,551
Net loss	—	—	—	—	—	(1,364,518)	(1,364,518)
Balance at December 31, 2017	8,306,278	—	967,976	968	82,783,865	(61,554,889)	21,229,944
Conversion of Series A convertible preferred stock to common stock	(8,306,278)	—	553,752	554	(554)	—	—
Issuance of common stock to Series A convertible preferred stockholders under make-whole adjustment feature	—	—	777,895	778	(778)	—	—
Issuance of common stock related to accrued dividends	—	—	68,815	69	1,148,238	—	1,148,307
Series A cumulative preferred dividend	—	—	—	—	(85,993)	—	(85,993)
Issuance of common stock and warrants, net of issuance costs	—	—	1,000,000	1,000	10,416,520	—	10,417,520
Common stock issued for advisory services	—	—	7,792	8	49,992	—	50,000
Stock-based compensation expense	—	—	—	—	1,221,591	—	1,221,591
Net loss	—	—	—	—	—	(18,369,810)	(18,369,810)
Balance at December 31, 2018	—	\$ —	3,376,230	\$ 3,377	\$ 95,532,881	\$ (79,924,699)	\$ 15,611,559

(a) In 2017, the Company adopted provisions of ASU 2016-09, *Improvements to Employee Share Based Payment Accounting*, resulting in a cumulative effect adjustment to Accumulated Deficit and Additional Paid-in Capital for previously unrecognized stock-based compensation expense.

See accompanying notes to consolidated financial statements.

DIFFUSION PHARMACEUTICALS INC.
CONSOLIDATED STATEMENTS OF CASH FLOW

	Year Ended December 31,	
	2018	2017
Operating activities:		
Net loss	\$ (18,369,810)	\$ (1,364,518)
Adjustments to reconcile net loss to net cash used in operating activities:		
Depreciation	110,371	67,981
Stock-based compensation expense	1,221,591	1,240,551
Common stock issued for advisory services	50,000	50,000
Warrant related expense, change in fair value, and other financing expenses	—	(8,976,250)
Change in deferred income taxes	(437,289)	(1,055,685)
Goodwill impairment	6,929,258	—
Non-cash interest expense, net	—	33,517
Changes in operating assets and liabilities:		
Prepaid expenses, deposits and other assets	(1,102)	(664,162)
Accounts payable, accrued expenses and other liabilities	(275,835)	(1,663,789)
Net cash used in operating activities	(10,772,816)	(12,332,355)
Cash flows used in investing activities:		
Purchases of property and equipment	—	(447,823)
Purchases of certificates of deposit	—	(10,000,000)
Maturities of certificates of deposit	—	10,000,000
Net cash used in investing activities	—	(447,823)
Cash flows provided by financing activities:		
Proceeds from sale of common stock	10,846,062	—
Proceeds from the sale of Series A convertible preferred stock and warrants, net	—	22,129,774
Repayment of convertible debt	(550,000)	(1,880,000)
Payment of offering costs	(428,542)	(125,980)
Net cash provided by financing activities	9,867,520	20,123,794
Net (decrease) increase in cash and cash equivalents	(905,296)	7,343,616
Cash and cash equivalents at beginning of year	8,896,468	1,552,852
Cash and cash equivalents at end of year	<u>\$ 7,991,172</u>	<u>\$ 8,896,468</u>
Supplemental disclosure of cash flow information:		
Cash paid for interest	\$ 40,142	\$ 112,800
Supplemental disclosure of non-cash investing and financing activities:		
Reclassification of accrued dividends related to the issuance of common stock to Series A convertible preferred stock holders	\$ 1,148,307	\$ —
Reclassification of the fair market value of the Series A warrants	\$ —	\$ 13,153,524
Series A cumulative preferred dividends	\$ 85,993	\$ 1,252,394
Conversion of accrued dividends related to convertible preferred stock	\$ —	\$ 190,080
Offering costs in accounts payable and accrued expenses	\$ —	\$ 146,776

See accompanying notes to consolidated financial statements.

DIFFUSION PHARMACEUTICALS INC.
NOTES TO CONSOLIDATED FINANCIAL STATEMENTS

1. Organization and Description of Business

Diffusion Pharmaceuticals Inc. (“Diffusion” or the “Company”), a Delaware corporation, is a clinical stage biotechnology company developing new treatments for life threatening conditions by improving the body’s ability to bring oxygen to the areas where it is needed most. The Company is developing its lead product candidate, transcrocetinate sodium, also known as trans sodium crocetininate (“TSC”), for use in those life threatening conditions in which cellular oxygen deprivation (“hypoxia”) is the basis for significant unmet medical needs. TSC is designed to safely and selectively target and re-oxygenate the micro-environment of hypoxic cells, and can potentially be used in many indications, including oncology and cardiovascular/stroke. In cancer, TSC re-oxygenates treatment-resistant cancerous tissue, making the cancer cells up to three times more susceptible to the therapeutic effects of standard-of-care radiation therapy and chemotherapy. In stroke, TSC helps promote the diffusion of oxygen into those brain cells in which oxygen-deprivation causes neuronal death resulting in patient mortality or morbidity. In addition to the TSC programs, the Company is exploring alternatives regarding how best to capitalize upon our product candidate RES-529, which may include possible out-licensing and other options. RES-529 is a novel PI3K/Akt/mTOR pathway inhibitor which has completed two Phase 1 clinical trials for age-related macular degeneration and was in preclinical development in oncology, specifically GBM. RES-529 has shown activity in both in vitro and in vivo glioblastoma animal models and has been demonstrated to be orally bioavailable and capable of crossing the blood brain barrier.

On December 13, 2018, the Company effected a 1-for-15 reverse split of its common stock. As a result of the reverse stock split, every fifteen shares of common stock outstanding immediately prior to the reverse stock split were reclassified and combined into one share of Common Stock. No fractional shares were issued in connection with the reverse stock split. Stockholders who otherwise would have been entitled to receive fractional shares of common stock had their holdings rounded up to the next whole share. Proportional adjustments were made to the Company’s outstanding warrants, stock options and other equity securities and to the Company’s 2015 Equity Incentive Plan, as amended, to reflect the reverse stock split, in each case, in accordance with the terms thereof. The accompanying consolidated financial statements and these notes give retroactive effect to this reverse stock split.

2. Liquidity

The Company has not generated any revenues from product sales and has funded operations primarily from the proceeds of public offerings, convertible debt and convertible preferred stock. Substantial additional financing will be required by the Company to continue to fund its research and development activities. No assurance can be given that any such financing will be available when needed or that the Company’s research and development efforts will be successful.

The Company regularly explores alternative means of financing its operations and seeks funding through various sources, including public and private securities offerings, collaborative arrangements with third parties and other strategic alliances and business transactions. On January 22, 2018, the Company closed an underwritten public offering of 1,000,000 shares of the Company’s common stock, par value \$0.001 per share (“Common Stock”) and warrants to purchase 1,000,000 shares of Common Stock. At the closing, the Company also issued warrants to purchase an additional 131,375 shares of Common Stock pursuant to the underwriter’s partial exercise of its overallotment option. The shares of Common Stock and warrants were sold at a combined public offering price of \$12.00 per share and warrant for total proceeds of approximately \$10.8 million. The warrants have an exercise price of \$12.00 per share and a term of five years from the date of issuance. In addition, at the closing, the Company issued to designees of the underwriter of the offering warrants to purchase up to 50,000 shares of Common Stock. The underwriter’s warrants have an exercise price of \$15.00, a term of five years from the date of issuance and otherwise substantially similar terms to the form of investor warrant. As a result of the offering, all outstanding shares of the Company’s Series A convertible preferred stock converted into 1,400,462 shares of Common Stock (including accrued dividends on the Series A convertible preferred stock paid-in-kind and issuance of shares of Common Stock in respect of the “make-whole” adjustment feature thereof).

The Company currently does not have any commitments to obtain additional funds and may be unable to obtain sufficient funding in the future on acceptable terms, if at all. If the Company cannot obtain the necessary funding, it will need to delay, scale back or eliminate some or all of its research and development programs or enter into collaborations with third parties to: commercialize potential products or technologies that it might otherwise seek to develop or commercialize independently; consider other various strategic alternatives, including a merger or sale of the Company; or cease operations. If the Company engages in collaborations, it may receive lower consideration upon commercialization of such products than if it had not entered into such arrangements or if it entered into such arrangements at later stages in the product development process.

DIFFUSION PHARMACEUTICALS INC.
NOTES TO CONSOLIDATED FINANCIAL STATEMENTS
CONTINUED

The Company has prepared its financial statements assuming that it will continue as a going concern, which contemplates realization of assets and the satisfaction of liabilities in the normal course of business. The Company has incurred net losses since inception and it expects to generate losses from operations for the foreseeable future primarily due to research and development costs for its potential product candidates, which raises substantial doubt about the Company's ability to continue as a going concern. The Company currently has no sources of revenue and its ability to continue as a going concern is dependent on its ability to raise capital to fund its future business plans. Additionally, volatility in the capital markets and general economic conditions in the United States may be a significant obstacle to raising the required funds. These factors raise substantial doubt about its ability to continue as a going concern. The financial statements included herein do not include any adjustments that might be necessary should the Company be unable to continue as a going concern. If the going concern basis were not appropriate for these financial statements, adjustments would be necessary in the carrying value of assets and liabilities, the reported expenses and the balance sheet classifications used.

Operations of the Company are subject to certain risks and uncertainties including various internal and external factors that will affect whether and when the Company's product candidates become approved drugs and how significant their market share will be, some of which are outside of the Company's control. The length of time and cost of developing and commercializing these product candidates and/or failure of them at any stage of the drug approval process will materially affect the Company's financial condition and future operations. The Company believes its cash and cash equivalents as of December 31, 2018 are sufficient to fund operations into July 2019.

3. Basis of Presentation and Summary of Significant Accounting Policies

Basis of Presentation

The accompanying consolidated financial statements of the Company have been prepared in accordance with US GAAP. Any reference in these notes to applicable guidance is meant to refer to US GAAP as found in the Accounting Standards Codification ("ASC") and Accounting Standards Updates ("ASU") of the Financial Accounting Standards Board ("FASB").

Use of Estimates

The preparation of financial statements in conformity with US GAAP requires the Company to make estimates and assumptions that affect the reported amounts of assets and liabilities and disclosure of contingent assets and liabilities at the date of the financial statements and the reported amounts of expenses during the reporting period.

On an ongoing basis, the Company evaluates its estimates using historical experience and other factors, including the current economic environment. Significant items subject to such estimates are assumptions used for purposes of determining stock-based compensation, the fair value of the warrants, the fair value of the convertible notes, and accounting for research and development activities. Management believes its estimates to be reasonable under the circumstances. Actual results could differ significantly from those estimates.

Fair Value of Financial Instruments

The carrying amounts of the Company's financial instruments, including cash equivalents, accounts payable, and accrued expenses approximate fair value due to the short-term nature of those instruments. As of December 31, 2017, the fair value of the Company's outstanding Series B convertible note was approximately \$0.6 million. The fair value of the convertible note was determined using a binomial lattice model that utilizes certain unobservable inputs that fall within Level 3 of the fair value hierarchy. All amounts outstanding under the Series B convertible note were repaid during the year ended December 31, 2018.

DIFFUSION PHARMACEUTICALS INC.
NOTES TO CONSOLIDATED FINANCIAL STATEMENTS

Concentration of Credit Risk

Financial instruments that potentially expose the Company to concentrations of credit risk consist principally of cash on deposit with multiple financial institutions, the balances of which frequently exceed federally insured limits.

Cash and Cash Equivalents

The Company considers any highly liquid investments, such as money market funds, with an original maturity of three months or less to be cash and cash equivalents.

Property and Equipment

The Company records property and equipment at cost less accumulated depreciation and amortization. Costs of renewals and improvements that extend the useful lives of the assets are capitalized. Maintenance and repairs are expensed as incurred. Depreciation is recognized on a straight-line basis over the estimated useful lives of the assets, which generally range from 2 to 15 years. The Company amortizes leasehold improvements over the shorter of the estimated useful life of the asset or the term of the related lease. Upon retirement or disposition of assets, the costs and related accumulated depreciation and amortization are removed from the accounts with the resulting gains or losses, if any, reflected in results of operations.

Long-Lived Assets

Long-lived assets are reviewed for potential impairment whenever events indicate that the carrying amount of such assets may not be recoverable. The Company does this by comparing the carrying value of the long-lived assets with the estimated future undiscounted cash flows expected to result from the use of the assets, including cash flows from disposition. If it is determined an impairment exists, the asset is written down to its estimated fair value. The Company has not recognized any impairment of long-lived assets during the years ended December 31, 2018 and 2017.

Goodwill and Intangible Assets

Goodwill and intangible assets deemed to have indefinite lives are not amortized but rather are tested at least annually for impairment, or when circumstances indicate that the carrying amount of the asset may not be recoverable. If the carrying value of the reporting unit exceeds fair value, goodwill is considered impaired. In January 2017, the FASB issued revised guidance that simplifies the test for goodwill impairment, effective for fiscal years beginning after December 15, 2019, with early adoption permitted. The Company early adopted this standard in the third quarter of 2018. Under the revised guidance, if a reporting unit's carrying value exceeds its fair value, an impairment charge will be recorded to reduce the reporting unit to fair value. The Company has a single reporting unit and all goodwill relates to that reporting unit. The Company's RES-529 intangible asset and goodwill are assessed for impairment annually on October 1 of the Company's fiscal year or more frequently if impairment indicators exist. There was no impairment to the Company's RES-529 intangible asset recognized during the years ended December 31, 2018 and 2017. During the year ended December 31, 2018, the Company recorded a non-cash goodwill impairment charge of \$6.9 million (see Note 5).

Research and Development

Major components of research and development costs include internal research and development (such as salaries and related employee benefits, equity-based compensation, supplies and allocated facility costs) and contracted services (research and development activities performed on the Company's behalf). Costs incurred for research and development are expensed as incurred.

At the end of the reporting period, the Company compares payments made to third-party service providers to the estimated progress toward completion of the research or development objectives. Such estimates are subject to change as additional information becomes available. Depending on the timing of payments to the service providers and the progress that the Company estimates has been made as a result of the services provided, the Company may record net prepaid or accrued expenses relating to these costs.

DIFFUSION PHARMACEUTICALS INC.
NOTES TO CONSOLIDATED FINANCIAL STATEMENTS

Upfront payments made to third parties who perform research and development services on the Company's behalf are expensed as services are rendered.

Patent Costs

Patent costs, including related legal costs, are expensed as incurred and are recorded within general and administrative expenses in the statements of operations.

Income Taxes

As a corporation, the Company uses the asset and liability method of accounting for income taxes. Deferred tax assets and liabilities are recognized for the estimated future tax consequences attributable to differences between the financial statement carrying amounts of existing assets and liabilities and their respective tax bases and operating loss and credit carryforwards. Deferred tax assets and liabilities are measured using enacted tax rates expected to apply to taxable income in the years in which those temporary differences are expected to be recovered or settled. A valuation allowance is provided when it is more likely than not that some portion or all of a deferred tax asset will not be realized. The Company recognizes the benefit of an uncertain tax position that it has taken or expects to take on its income tax return it files, if such a position is more likely than not to be sustained.

Stock-based Compensation

The Company measures employee and nonemployee stock-based awards at grant-date fair value and records compensation expense on a straight-line basis over the vesting period of the award. Stock-based awards issued to non-employees are revalued until the award vests. The Company uses the Black-Scholes option pricing model to value its stock option awards. Estimating the fair value of stock option awards requires management to apply judgment and make estimates, including the volatility of the Company's common stock, the expected term of the Company's stock options, the expected dividend yield and the fair value of the Company's common stock on the measurement date. As a result, if factors change and management uses different assumptions, stock-based compensation expense could be materially different for future awards.

The expected term of stock options was estimated using the "simplified method" for employee options as the Company has no historical information to develop reasonable expectations about future exercise patterns and post vesting employment termination behavior for its stock option grants. The simplified method is based on the average of the vesting tranches and the contractual life of each grant. For options granted to non-employees, the Company uses the remaining contractual life. For stock price volatility, the Company uses comparable public companies as a basis for its expected volatility to calculate the fair value of option grants. The Company assumes no dividend yield because dividends are not expected to be paid in the near future, which is consistent with the Company's history of not paying dividends. The risk-free interest rate is based on U.S. Treasury notes with a term approximating the expected life of the option. The Company no longer estimates forfeitures and accounts for forfeitures in the periods they occur.

DIFFUSION PHARMACEUTICALS INC.
NOTES TO CONSOLIDATED FINANCIAL STATEMENTS

Net Loss Per Share

Basic loss per share is computed by dividing net loss applicable to common stockholders by the weighted average number of shares of common stock outstanding during each period. For purposes of calculating diluted loss per common share, the denominator includes both the weighted average common shares outstanding and the number of common stock equivalents if the inclusion of such common stock equivalents would be dilutive. Dilutive common stock equivalents potentially include warrants, stock options and restricted stock awards using the treasury stock method and convertible debt using the “if-converted” method. The diluted loss per common share calculation is further affected by an add-back of change in fair value of warrant liability to the numerator under the assumption that the change in fair value of warrant liability would not have been incurred if the warrants had been converted into common stock.

	Year ended December 31,	
	2018	2017
Basic net loss per common share calculation:		
Net loss	\$ (18,369,810)	\$ (1,364,518)
Accretion of Series A cumulative preferred dividends	(85,993)	(1,252,394)
Deemed dividend related to the make-whole provision for the conversion of Series A convertible preferred stock into common stock	(8,167,895)	—
Net loss attributable to common stockholders	\$ (26,623,698)	\$ (2,616,912)
Weighted average shares outstanding, basic	3,242,301	827,575
Net loss per share of common, basic	\$ (8.21)	\$ (3.16)
Diluted net loss per common share calculation:		
Net loss attributable to common stockholders	(26,623,698)	(2,616,912)
Change in fair value of warrant liability	—	(22,072,322)
Diluted net loss	(26,623,698)	(24,689,234)
Weighted average common shares outstanding, basic	3,242,301	827,575
Common stock equivalents arising from warrants	—	20,515
Common stock equivalents	3,242,301	848,090
Net loss per share of common stock, diluted	\$ (8.21)	\$ (29.11)

The following potentially dilutive securities outstanding have been excluded from the computation of diluted weighted average shares outstanding, as they would be anti-dilutive:

	December 31,	
	2018	2017
Convertible debt	—	14,292
Common stock warrants	2,087,012	29,848
Convertible preferred stock	—	553,752
Stock options	203,736	170,461
Unvested restricted stock awards	—	204
	2,290,748	768,557

Amounts in the table reflect the common stock equivalents of the noted instruments.

Comprehensive Loss

The Company has no items of comprehensive income or loss other than net loss.

DIFFUSION PHARMACEUTICALS INC.
NOTES TO CONSOLIDATED FINANCIAL STATEMENTS

Recently Issued But Not Yet Adopted Accounting Pronouncements

In August 2018, the FASB issued ASU 2018-13, *Disclosure Framework-Changes to the Disclosure Requirements for Fair Value Measurements*, which changes the fair value measurement disclosure requirements of ASC 820. The goal of the ASU is to improve the effectiveness of ASC 820's disclosure requirements by providing users of the financial statements with better information about assets and liabilities measured at fair value in the financial statements and notes thereto. The guidance is applicable to public business entities for fiscal years beginning after December 15, 2019 and interim periods within those years. The Company is currently evaluating the potential impact of the adoption of this standard on its related disclosures.

In July 2017, the FASB issued ASU 2017-11, *Earnings Per Share (Topic 260); Distinguishing Liabilities from Equity (Topic 480); Derivatives and Hedging (Topic 815): (Part I) Accounting for Certain Financial Instruments with Down Round Features, (Part II) Replacement of the Indefinite Deferral for Mandatorily Redeemable Financial Instruments of Certain Nonpublic Entities and Certain Mandatorily Redeemable Noncontrolling Interests with a Scope Exception*. The first part of this update addresses the complexity of accounting for certain financial instruments with down round features and the second part addresses the complexity of distinguishing liabilities from equity. The guidance is applicable to public business entities for fiscal years beginning after December 15, 2018 and interim periods within those years. The Company is currently evaluating the potential impact of the adoption of this standard on its consolidated results of operations, financial position and cash flows and related disclosures.

In February 2016, the FASB issued ASU 2016-02, *Leases (Topic 842)*. Under the new guidance, lessees are required to record a right-of-use (ROU) asset and a lease liability for all leases with a term greater than 12 months, measured on a discounted basis. Leases with a term of 12 months or less will be accounted for similar to existing guidance for operating leases. ASC 842 will be effective for the Company on January 1, 2019, and the Company expects to apply the practical expedients allowed by the standard, mainly related to the reassessment of expired or existing leases. See Note 8 for details of the Company's current lease arrangement. Although management continues to evaluate the effect to the Company's Consolidated Financial Statements and disclosures, management currently estimates total assets and liabilities will increase approximately \$0.3 million to \$0.4 million upon adoption. Management does not expect a material impact to the Company's Consolidated Statements of Operations or Consolidated Statements of Cash Flows.

Recently Adopted Accounting Pronouncements

In January 2017, the FASB issued ASU 2017-04, *Intangibles-Goodwill and Other (Topic 350)* which simplifies the accounting for goodwill impairments by eliminating step 2 from the goodwill impairment test. Instead, if the carrying amount of a reporting unit exceeds its fair value, an impairment loss shall be recognized in an amount equal to that excess, limited to the total amount of goodwill allocated to that reporting unit. The standard will be effective for fiscal years beginning after December 15, 2019, including interim periods within such fiscal years. Early adoption is allowed for all entities as of January 1, 2017, for annual and any interim impairment tests occurring on or after January 1, 2017. The Company early adopted this standard in the third quarter of 2018. See Note 5 for further discussion of the Company's intangible assets, including goodwill.

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In March 2016, the FASB issued ASU 2016-09, *Compensation – Improvements to Employee Share-Based Payment Accounting*, which simplifies several aspects of the accounting for employee share-based payment transactions including the accounting for income taxes, forfeitures, and statutory tax withholding requirements, as well as classification in the statement of cash flows. The guidance is applicable to public business entities for fiscal years beginning after December 15, 2016 and interim periods within those years. The Company adopted this standard in 2017 by electing to account for forfeitures in the period that they occur. Under ASU 2016-09, accounting changes adopted using the modified retrospective method must be calculated as of the beginning of the period adopted and reported as a cumulative-effect adjustment. As a result, the Company recognized cumulative-effect adjustment of approximately \$1,000 on January 1, 2017.

4. Property and Equipment

Property and equipment consists of the following:

	December 31,	
	2018	2017
Laboratory equipment	\$ 182,357	\$ 182,357
Furniture and office equipment	155,113	155,113
Leasehold improvements	430,000	430,000
Total property and equipment	767,470	767,470
Less: accumulated depreciation	(417,189)	(306,818)
Property and equipment, net	\$ 350,281	\$ 460,652

Depreciation expense was approximately \$0.1 million and \$68,000 for the years ended December 31, 2018 and 2017, respectively.

5. Goodwill and Intangible Assets

Goodwill is the excess of the cost of an acquired entity over the net amounts assigned to tangible and intangible assets acquired and liabilities assumed. The Company applies ASC 350 “*Goodwill and Other Intangible Assets*,” which requires testing goodwill for impairment on an annual basis. The Company evaluates goodwill on a consolidated basis as the Company is organized as a single reporting unit. The Company completes its annual impairment test on October 1 each year, or more frequently if triggering events indicate a possible impairment. The Company considers certain triggering events when evaluating whether an interim goodwill impairment analysis is warranted. Among these would be a significant long-term decrease in the market capitalization of the Company. The Company’s market capitalization was below the carrying value of equity throughout the third quarter of 2018 and as a result, management concluded that the carrying value of goodwill may not be recoverable and that a triggering event requiring an interim assessment of goodwill impairment had occurred during the three months ended September 30, 2018.

Management performed the goodwill impairment assessment using a market approach to estimate the fair value of the Company using the Company’s market capitalization. This fair value was derived by multiplying the Company’s shares outstanding by the average daily close prices of the Company’s stock during the third quarter of 2018. The carrying value of the Company’s net equity exceeded its fair value, and accordingly, the Company recognized a \$4.2 million non-cash impairment charge to goodwill that reduced the carrying value to fair value. During the fourth quarter of 2018, this downward trend of the Company’s market capitalization continued, and the Company performed another goodwill impairment assessment using a market approach to estimate the fair value of the Company. This fair value was derived by multiplying the Company’s shares outstanding by the average daily close prices of the Company’s stock during the fourth quarter. The carrying value of the Company’s net equity exceeded its fair value, and accordingly, the Company recognized an additional \$2.7 million non-cash impairment charge to goodwill. As a result of these impairment charges, the Company has no goodwill remaining on its consolidated balance sheet as of December 31, 2018.

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The Company has an indefinite-lived In-Process Research and Development Asset (IPR&D) called RES-529, which has a balance of \$8.6 million at both December 31, 2018 and December 31, 2017. RES-529 is a PI3K/Akt/mTOR pathway inhibitor in preclinical development for oncology. There was no impairment to the Company's RES-529 intangible asset recognized during the years ended December 31, 2018 or 2017.

6. Accrued Expenses and Other Current Liabilities

Accrued expenses and other current liabilities consist of the following:

	December 31,	
	2018	2017
Accrued interest payable	\$ —	\$ 37,415
Accrued Series A convertible preferred stock dividends	—	1,062,314
Accrued payroll and payroll related expenses	409,889	312,221
Accrued professional fees	69,231	122,711
Accrued clinical studies expenses	34,000	63,350
Other	92,106	30,840
Total	\$ 605,226	\$ 1,628,851

7. Convertible Debt

The components of debt outstanding at December 31, 2017 was as follows:

	December 31, 2017
Series B convertible notes	550,000
Less current portion	(550,000)
Long-term debt, net of current portion	<u>\$ —</u>

Upon maturity of the Series B convertible debt during the second quarter of 2018, the Company repaid the outstanding principal and interest of approximately \$0.6 million and \$40,000, respectively. As such, the Company does not have any debt outstanding as of December 31, 2018. For the years ended December 31, 2018 and 2017, the Company recognized interest expense of approximately \$3,000 and \$0.1 million, respectively in connection with its convertible debt instruments. Accrued interest was \$37,000 as of December 31, 2017.

8. Commitments and Contingencies

Office Space Lease Commitment

The Company leases office and laboratory facilities in Charlottesville, Virginia. Rent expense related to the Company's operating lease for both the years ended December 31, 2018 and 2017 was approximately \$0.1 million. Future minimum rental payments under the Company's non-cancelable operating lease at December 31, 2018 were as follows:

	Rental Commitments
2019	\$ 114,409
2020	116,464
2021	118,519
2022	39,735
Total	\$ 389,127

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Arrangements with Clinical Research Organization

The Company has various agreements with contract research organizations (“CROs”) to provide clinical trial services for individual studies and projects by executing individual work orders governed by Master Service Arrangements (“MSAs”). The MSAs and associated work orders are designed such that quarterly payments are to be made in advance of the work to be performed. The Company recognized research and development expenses related to these MSAs of \$1.6 million and \$1.0 million during the years ended December 31, 2018 and 2017, respectively. As of December 31, 2018, there was \$0.8 million of prepaid research and development costs that are estimated to be recognized during fiscal 2019.

Legal Proceedings

On August 7, 2014, a complaint was filed in the Superior Court of Los Angeles County, California by Paul Feller, the Company’s former Chief Executive Officer under the caption *Paul Feller v. RestorGenex Corporation, Pro Sports & Entertainment, Inc., ProElite, Inc. and Stratus Media Group, GmbH* (Case No. BC553996). The complaint asserts various causes of action, including, among other things, promissory fraud, negligent misrepresentation, breach of contract, breach of employment agreement, breach of the covenant of good faith and fair dealing, violations of the California Labor Code and common counts. The plaintiff is seeking, among other things, compensatory damages in an undetermined amount, punitive damages, accrued interest and an award of attorneys’ fees and costs. On December 30, 2014, the Company filed a petition to compel arbitration and a motion to stay the action. On April 1, 2015, the plaintiff filed a petition in opposition to the Company’s petition to compel arbitration and a motion to stay the action. After a hearing for the petition and motion on April 14, 2015, the Court granted the Company’s petition to compel arbitration and a motion to stay the action. On January 8, 2016, the plaintiff filed an arbitration demand with the American Arbitration Association. On November 19, 2018 at an Order to Show Cause Re Dismissal Hearing, the Court found sufficient grounds not to dismiss the case, and an arbitration hearing has been scheduled for November 2019. The Company believes this matter is without merit and intends to defend the arbitration vigorously. Because this matter is in an early stage, the Company is unable to predict its outcome and the possible loss or range of loss, if any, associated with its resolution or any potential effect the matter may have on the Company’s financial position. Depending on the outcome or resolution of this matter, it could have a material effect on the Company’s financial position.

9. Convertible Preferred Stock, Stockholders’ Equity and Common Stock Warrants

2018 Common Stock Offering

In January 2018, the Company entered into an Underwriting Agreement (the “Agreement”) pursuant to which it issued 1,000,000 shares of Common Stock and warrants to purchase 1,000,000 shares of Common Stock with an initial exercise price of \$12.00 per share for cash proceeds of \$10.8 million. In addition, as compensation for its services, the Company granted to the underwriter in the transaction an option (the “Over-Allotment Option”) to purchase, in the aggregate, 150,000 shares of Common Stock (the “Option Shares”) and warrants to purchase up to 150,000 shares of Common Stock (the “Option Warrants”). The underwriter exercised its right to purchase a portion of the Option Warrants and received an additional 131,375 warrants to purchase Common Stock with an initial exercise price \$12.00 per share.

In addition, at the closing, the Company issued to designees of the underwriter warrants to purchase up to 50,000 shares of Common Stock. The underwriter’s warrants have an exercise price of \$15.00 per share, a term of five years from the date of issuance and otherwise substantially similar terms to the form of the investor warrant.

During its evaluation of equity classification for the Common Stock warrants, the Company considered the conditions as prescribed within ASC 815-40, *Derivatives and Hedging, Contracts in an Entity’s own Equity* (“ASC 815-40”). The conditions within ASC 815-40 are not subject to a probability assessment. The warrants do not fall under the liability criteria within ASC 480 *Distinguishing Liabilities from Equity* as they are not puttable and do not represent an instrument that has a redeemable underlying security. The warrants do meet the definition of a derivative instrument under ASC 815, but are eligible for the scope exception as they are indexed to the Company’s own stock and would be classified in permanent equity if freestanding.

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As a result of the Company's Common Stock offering in January 2018, all outstanding shares of the Company's Series A convertible preferred stock (discussed below) converted into 1,400,462 shares of Common Stock of which (i) 553,752 shares were issued for the automatic conversion of Series A convertible preferred stock (ii) 68,815 shares were issued upon settlement of accrued dividends and (iii) 777,895 shares were issued for the settlement of the "make-whole" adjustment feature. A deemed dividend of \$8.2 million was recognized for the value of the common shares issued for the settlement of the make-whole adjustment feature.

Series A Convertible Preferred Stock

In March 2017, the Company completed a \$25.0 million private placement of its securities in which the Company offered and sold units consisting of one share of the Company's Series A convertible preferred stock and a warrant to purchase one share of Common Stock for each share of Series A convertible preferred stock purchased in the private placement (the "2017 Private Placement"). Each share of Series A convertible preferred stock entitled the holder to an 8.0% cumulative dividend payable in shares of Common Stock. The holders, at their option, were able to convert each share of Series A convertible preferred stock into one share of the Company's Common Stock based on the initial conversion price of \$30.30 per share, subject to adjustment. Each warrant entitles the holder to purchase one share of Common Stock at an initial exercise price of \$33.30, subject to adjustment and expires on the fifth anniversary of their original issuance date.

The Company sold 12,376,329 units in the 2017 Private Placement and received approximately \$22.1 million in aggregate net cash proceeds, after deducting commissions and other expenses of approximately \$2.9 million. In addition, as compensation for its services, the Company granted to its placement agent in the 2017 Private Placement warrants to purchase an aggregate of 78,637 shares of Common Stock at an initial exercise price of \$33.30 per share, which expire on the fifth anniversary of their original issuance date.

During its evaluation of equity classification for the common stock warrants, the Company considered the conditions as prescribed within ASC 815-40. The conditions within ASC 815-40 are not subject to a probability assessment. As the Company was obligated to issue a variable number of shares to settle the cumulative dividends on the Series A convertible preferred stock, the Company could not assert that there would be sufficient authorized shares available to settle the warrants issued in connection with the Series A offering. Accordingly, these warrants were classified as liabilities. In November 2017 the Company effected an amendment to its Certificate of Incorporation to permit the Company to pay dividends on the Company's Series A Convertible Preferred Stock in either cash or shares of the Company's Common Stock, which was approved by the stockholders. As a result of this amendment, the warrants were reclassified on the consolidated balance sheet from liabilities to stockholders' equity in the fourth quarter of 2017.

As the fair value of the warrants upon their issuance was in excess of the proceeds of the 2017 Private Placement, there were no proceeds allocated to the Series A convertible preferred stock. The excess fair value of the warrants over the gross proceeds of the 2017 Private Placement and the fair value of the warrants granted to its placement agent was \$10.2 million in the aggregate and were recorded as warrant related expenses in the Company's consolidated statement of operations for the year ended December 31, 2017.

In contemplation of completing the 2017 Private Placement, pursuant to the Company's Certificate of Incorporation, on March 13, 2017, the Company adopted the Certificate of Designations of Preferences, Rights and Limitations of the Series A Convertible Preferred Stock of the Company, authorizing 13,750,000 shares of Series A Convertible Preferred Stock for issuance. Upon the mandatory conversion of all of the shares of Series A Convertible Preferred Stock into our Common Stock during 2018, no shares of Series A Convertible Preferred Stock remained authorized, issued or outstanding.

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Common Stock

In addition to the above offerings of Common Stock, during the years ended December 31, 2018 and 2017, respectively, the Company issued 7,792 and 1,174 shares, respectively, for advisory services. The Company did not purchase or retire any shares of its Common Stock during the years ended December 31, 2018 and 2017.

Common Stock Warrants

As of December 31, 2018, the Company had the following warrants outstanding to acquire shares of its common stock:

	Outstanding	Range of exercise price per share		Expiration dates
Common stock warrants issued prior to 2016	1,767	\$562.50	-	\$735.00 2019
Common stock warrants issued in 2017 related to Series A convertible preferred stock offering	903,870	\$33.30		March 2022
Common stock warrants issued in 2018 related to the common stock offering	1,181,375	\$12.00	-	\$15.00 January 2023
	<u>2,087,012</u>			

During the years ended December 31, 2018 and 2017, 28,123 and 867 warrants issued prior to 2016 expired, respectively.

10. Stock-Based Compensation

2015 Equity Plan

The 2015 Equity Incentive Plan of the Company, as amended in July 2016, currently allows for the issuance of up to a maximum of 33,333 shares of common stock in connection with the grant of stock-based awards, including stock options, restricted stock, restricted stock units, stock appreciation rights and other types of awards as deemed appropriate, not including shares subject to awards assumed in connection with certain transactions. As of December 31, 2018, there were 1,814 shares of Common Stock available for future issuance under the 2015 Equity Incentive Plan. In addition, beginning on January 1, 2017, on each January 1st through the term of the plan, up to 4.0% of the total shares of the Company's common stock outstanding as of December 31st will be added to the plan reserve, unless a lesser amount is stipulated by the Compensation Committee of the Company's Board of Directors. On January 1, 2019, the maximum number of shares of the 2015 Equity Incentive Plan increased by 135,049 shares, or 4.0% of the total shares of the Company's common stock outstanding at December 31, 2018.

The Company recorded stock-based compensation expense in the following expense categories of its consolidated statements of operations for the periods indicated:

	Year ended December 31,	
	2018	2017
Research and development	\$ 62,161	\$ 674,643
General and administrative	1,159,430	716,425
Total stock-based compensation expense	<u>\$ 1,221,591</u>	<u>\$ 1,391,068</u>

DIFFUSION PHARMACEUTICALS INC.
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The following table summarizes the activity related to all stock option grants to employees and non-employees:

	Number of Options	Weighted average exercise price per share	Weighted average remaining contractual life (in years)	Aggregate Intrinsic Value
Balance at January 1, 2017	147,214	\$ 121.37		
Granted	23,345	36.92		
Expired	(98)	225.00		
Balance at January 1, 2018	170,461	\$ 109.74	7.13	\$ 4,746
Granted	44,005	15.37		
Forfeited	(10,583)	131.25		
Expired	(147)	256.50		
Outstanding at December 31, 2018	203,736	\$ 88.14	6.70	\$ 143
Exercisable at December 31, 2018	167,585	\$ 101.69	6.25	\$ 143
Vested and expected to vest at December 31, 2018	203,736	\$ 88.14	6.70	\$ 143

Generally, the options have a ten (10) year contractual term and vest in equal monthly installments over three (3) years.

Non-employee Stock Options

Non-employee options are remeasured to fair value each period through operations using a Black-Scholes option-pricing model until the options vest. There were no options granted to non-employees during the year ended December 31, 2018 and there were 626 stock options granted to non-employees during the year ended December 31, 2017. The total fair value of non-employee stock options vested during the years ended December 31, 2018 and 2017 was approximately \$4,000 and \$90,000, respectively. At December 31, 2018, there was less than \$1,000 of unrecognized compensation cost related to 219 unvested stock options and subject to re-measurement until vested. The total unrecognized compensation expense will be recognized as expense over a weighted-average period of 1.16 years.

Employee Stock Options

The weighted average grant date fair value of stock option awards granted to employees was \$12.63 and \$30.43 during the years ended December 31, 2018 and 2017, respectively. The total fair value of options vested during the years ended December 31, 2018 and 2017 were \$1.2 million and \$1.1 million, respectively. No options were exercised during any of the periods presented. At December 31, 2018, there was \$0.6 million of unrecognized compensation cost related to unvested options that will be recognized as expense over a weighted-average period of 1.4 years.

The grant date fair value of employee stock options is determined using the Black-Scholes model. The following assumptions were used during the years ended December 31, 2018 and 2017:

	2018		2017	
Expected term (in years)	5.27	— 5.66	5.27	— 6.00
Risk-free interest rate	2.3%	— 2.8%	1.8%	— 2.4%
Expected volatility	113.6%	— 115.0%	109.8%	— 136.7%
Dividend yield	—	—	—	—

Restricted Stock Awards

As of December 31, 2018, there were no unvested shares of restricted stock. During the year ended December 31, 2018 and 2017, 204 and 409 shares vested, respectively. The fair value as of the respective vesting dates of the restricted stock awards was \$6,000 and \$12,000 for 2018 and 2017, respectively. There were no restricted stock awards granted in 2018 or 2017.

11. Defined Contribution Retirement Plan

The Company has established a 401(k) defined contribution plan (the 401(k) Plan) that covers all employees who qualify under the terms of the plan. Eligible employees may elect to contribute to the 401(k) Plan up to 90% of their compensation, limited by the IRS-imposed maximum. The Company provides a safe harbor match with a maximum amount of 4% of the participant's compensation. The Company made matching contributions under the 401(k) Plan of approximately \$68,000 and \$49,000 for the years ended December 31, 2018 and 2017, respectively.

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12. Income Taxes

Deferred tax assets and liabilities are determined based on the differences between the financial statement carrying amounts and tax bases of assets and liabilities using enacted tax rates in effect for years in which differences are expected to reverse.

Significant components of the Company's deferred tax assets for federal income taxes consisted of the following:

Deferred tax assets	December 31, 2018	December 31, 2017
Net operating loss carryforwards	\$ 5,875,074	\$ 5,310,628
Stock option compensation	2,456,410	2,141,973
Orphan Drug credits	2,847,803	2,537,039
Capitalized start-up costs and other	7,349,092	5,247,468
Valuation allowance	(18,091,090)	(15,237,108)
Net deferred tax asset	<u>\$ 437,289</u>	
Deferred tax liabilities		
Intangible assets	(2,223,678)	(2,223,678)
Net deferred tax liability	<u>\$ (1,786,389)</u>	<u>\$ (2,223,678)</u>

The Company does not have unrecognized tax benefits as of December 31, 2018 or December 31, 2017. The Company recognizes interest and penalties accrued on any unrecognized tax benefits as a component of income tax expense.

The Company had net operating loss carryforwards ("NOL") for federal and state income tax purposes at December 31, 2018 of approximately:

Combined NOL Carryforwards:	December 31, 2018
Federal	\$ 22,819,972
State	22,845,568

The net operating loss carryforwards generated prior to 2017 begin expiring in 2034 for both federal and state income tax purposes. Those generated in 2018 and into the future now have an indefinite life. In January 2016, the Company increased the number of shares outstanding resulting in a change of ownership, under the provisions of Internal Revenue Code section 382 and similar state provisions. Stock issuances in 2018 and 2017 might have also resulted in changes of ownership. These provisions limit the Company's ability to utilize these net operating loss carryforwards to offset future income. The amounts above reflect the amount of NOLs that the Company expects to be able to utilize as a result of the limitation. Excluding the deferred tax asset associated with the net operating loss with unlimited carryforward, the Company recorded a valuation allowance for the remaining deferred tax assets as of December 31, 2018, because of the uncertainty of their realization.

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A reconciliation of income tax benefit at the statutory federal income tax rate and income taxes as reflected in the financial statements is as follows:

Rate reconciliation:	December 31, 2018	December 31, 2017
Federal tax benefit at statutory rate	(21.0)%	(34.0)%
State tax, net of Federal benefit	(2.9)%	(16.3)%
Change in fair value of warrant	— %	(126.1)%
Change in tax rate	— %	205.5 %
Goodwill impairment	7.7 %	— %
Orphan drug credit	(1.3)%	(36.0)%
Change in valuation allowance	15.2 %	(38.8)%
Stock compensation	— %	1.2 %
Other	— %	1.0 %
Total provision	(2.3)%	(43.5)%

The Company files income tax returns in the U.S. federal jurisdiction and various state jurisdictions. The Company's 2015 to 2017 tax years remain open and subject to examination; carryforward amounts from the 2014 year remain subject to adjustment.

On December 22, 2017 the President of the United States signed into law the Tax Cuts and Jobs Act ("The 2017 Tax Act"), which resulted in significant changes from previous tax law. The 2017 Tax Act required the Company to revalue its deferred tax assets and liabilities to the new rate of 21%. As a result of the change, the Company recorded a tax benefit of \$1.1 million for the year ended December 31, 2017. The 2017 Tax Act also changed the net operating loss carryforwards' period such that all net operating losses generated in 2018 and into the future now have an indefinite life. As a result of the change in net operating loss carryforward period, during the year ended December 31, 2018, the Company recognized an income tax benefit of \$0.4 million to reflect the adjustment allowed by the 2017 Tax Act to utilize indefinite deferred tax liabilities as a source of income against indefinite lived portions of the Company's deferred tax assets.

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13. Fair Value Measurements

Certain assets and liabilities are carried at fair value under GAAP. Fair value is defined as the exchange price that would be received for an asset or paid 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 on the measurement date. Valuation techniques used to measure fair value must maximize the use of observable inputs and minimize the use of unobservable inputs. Financial assets and liabilities carried at fair value are to be classified and disclosed in one of the following three levels of the fair value hierarchy, of which the first two are considered observable and the last is considered unobservable:

- Level 1—Quoted prices in active markets for identical assets or liabilities.
- Level 2—Observable inputs (other than Level 1 quoted prices), such as quoted prices in active markets for similar assets or liabilities, quoted prices in markets that are not active for identical or similar assets or liabilities, or other inputs that are observable or can be corroborated by observable market data.
- Level 3—Unobservable inputs that are supported by little or no market activity and that are significant to determining the fair value of the assets or liabilities, including pricing models, discounted cash flow methodologies and similar techniques.

The asset's or liability's fair value measurement level within the fair value hierarchy is based on the lowest level of any input that is significant to the fair value measurement.

The reconciliation of the common stock warrant liability measured at fair value on a recurring basis using significant unobservable inputs (Level 3) is as follows:

	Common Stock Warrant Liability
Balance at January 1, 2017	\$ —
Issued in connection with the Series A convertible preferred stock	35,225,846
Change in fair value	(22,072,322)
Reclassification of Series A warrants to additional paid in capital	(13,153,524)
Balance at December 31, 2017	\$ —

The common stock warrants issued in connection with the Series A convertible preferred stock were previously classified as liabilities on the Company's consolidated balance sheet, and were marked-to-market each reporting period with the change in fair value recorded as either income or expense in the accompanying consolidated statements of operations until the warrants were exercised, expired or other facts and circumstances lead the liability to be reclassified to stockholders' equity. In November 2017, the Company effected an amendment to its Certificate of Incorporation to permit the Company to pay dividends on the Company's Series A Convertible Preferred Stock in either cash or shares of the Company's Common Stock. As a result of this amendment, the warrants were reclassified on the consolidated balance sheet from liabilities to stockholders' equity in the fourth quarter of 2017.

The fair value of the warrant liability was estimated using the Black-Scholes model and assumptions used to value the warrant liability as of November 1, 2017, which was the date of the reclassification, were as follows:

Stock price	\$ 21.60
Exercise price	\$ 33.30
Expected term (in years)	4.38
Risk-free interest rate	1.9%
Expected volatility	104.1%
Dividend yield	—

14. Related Party Transactions

The Company's Director of Information Technologies is the son of the Chief Executive Officer and he has held that position since December 2014.

ITEM 9. CHANGES IN AND DISAGREEMENTS WITH ACCOUNTANTS ON ACCOUNTING AND FINANCIAL DISCLOSURE

None.

ITEM 9A. CONTROLS AND PROCEDURES

Evaluation of Disclosure Controls and Procedures

The term “disclosure controls and procedures” means our controls and other procedures that are designed to ensure that information required to be disclosed by us in the reports that we file or submit under the Securities Exchange Act of 1934, as amended, is recorded, processed, summarized and reported, within the time periods specified in the SEC’s rules and forms. Disclosure controls and procedures include, without limitation, controls and procedures designed to ensure that information required to be disclosed by us in the reports that we file or submit under the Exchange Act is accumulated and communicated to our management, including our principal executive officer and principal financial officer, or persons performing similar functions, as appropriate to allow timely decisions regarding required disclosure.

We carried out an evaluation, under the supervision and with the participation of our management, including our principal executive officer and principal financial officer, of the effectiveness of our disclosure controls and procedures (as defined in Exchange Act Rules 13a – 15(e) and 15d – 15(e)). Based upon that evaluation, our principal executive officer and principal financial officer concluded that, as of the end of the period covered in this report, our disclosure controls and procedures were effective to ensure that information required to be disclosed in reports filed under the Exchange Act is recorded, processed, summarized and reported within the required time periods and is accumulated and communicated to our management, including our principal executive officer and principal financial officer, as appropriate to allow timely decisions regarding required disclosure.

Our principal executive officer and principal financial officer do not expect that our disclosure controls or internal controls will prevent all error and all fraud. Although our disclosure controls and procedures were designed to provide reasonable assurance of achieving their objectives, a control system, no matter how well conceived and operated, can provide only reasonable, not absolute assurance that the objectives of the system are met. Further, the design of a control system must reflect the fact that there are resource constraints, and the benefits of controls must be considered relative to their costs. Because of the inherent limitations in all control systems, no evaluation of controls can provide absolute assurance that all control issues and instances of fraud, if any, within our company have been detected. These inherent limitations include the realities that judgments in decision-making can be faulty, and that breakdowns can occur because of a simple error or mistake. Additionally, controls can be circumvented if there exists in an individual a desire to do so. There can be no assurance that any design will succeed in achieving its stated goals under all potential future conditions.

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). Under the supervision and with the participation of our Chief Executive Officer and Senior Vice President, Finance, our management conducted an evaluation of the effectiveness of our internal control over financial reporting based on the framework in *Internal Control—Integrated Framework (2013)* issued by the Committee of Sponsoring Organizations of the Treadway Commission. Based on that evaluation, our management concluded that our internal control over financial reporting was effective as of December 31, 2018.

Attestation Report of the Independent Registered Public Accounting Firm

This report does not include an attestation report of our independent registered public accounting firm regarding internal control over financial reporting. Management's report was not subject to attestation by our independent registered public accounting firm pursuant to Section 989G of the Dodd-Frank Wall Street Reform and Consumer Protection Act, which exempts smaller reporting companies from the auditor attestation requirement.

Change in Internal Control Over Financial Reporting

There was no change in our internal control over financial reporting that occurred during our fourth quarter ended December 31, 2018 that has materially affected, or is reasonably likely to materially affect, our internal control over financial reporting.

ITEM 9B. OTHER INFORMATION

None.

PART III

ITEM 10. DIRECTORS, EXECUTIVE OFFICERS AND CORPORATE GOVERNANCE

The table below sets forth, as of March 19, 2019, certain information that has been furnished to us by each current director on the Company's board of directors (the "Board")

Name	Age	Director Since
David G. Kalergis	70	2016
John L. Gainer, Ph. D.	80	2016
Robert Adams ⁽¹⁾	68	2016
Mark T. Giles ⁽¹⁾	64	2016
Alan Levin ⁽¹⁾	56	2016

⁽¹⁾ Current member of the Audit, Compensation and Nominating and Corporate Governance Committees of the Board

The paragraphs below provide information about each current director, including all positions he holds, his principal occupation and business experience for the past five years, and the names of other publicly held companies of which he currently serves as a director or served as a director during the past five years. We believe that all of our director nominees display personal and professional integrity; satisfactory levels of education and/or business experience; broad-based business acumen; an appropriate level of understanding of our business and its industry and other industries relevant to our business; the ability and willingness to devote adequate time to the work of the Board and its committees; a fit of skills and personality with those of our other directors that helps build a board of directors that is effective, collegial and responsive to the needs of our company; strategic thinking and a willingness to share ideas; a diversity of experiences, expertise and background; and the ability to represent the interests of all of our stockholders. The information presented below regarding each director also sets forth specific experience, qualifications, attributes and skills that led the Board to the conclusion that he or she should serve as a director in light of our business and structure.

David G. Kalergis – Mr. Kalergis has served as our Chairman of the Board and Chief Executive Officer since January 2016. Mr. Kalergis, along with Dr. Gainer is the Company's co-founder and served as a director of Diffusion Pharmaceuticals LLC ("Diffusion LLC"), our predecessor, from its inception in 2001 through January 2016 and as its Chief Executive Officer from 2004 through January 2016. Prior to joining the Company, Mr. Kalergis held positions with the University of Virginia; as the general counsel and director of business development for Pharmaceutical Research Associates, Inc., a pharmaceutical contract research organization; as an intelligence analyst for the U.S. Government; and with the law firm Dewey, Ballantine, Bushby, Palmer & Wood, practicing in the areas of corporate finance, public offerings and mergers and acquisitions. In addition, from July 1998 until May 2012, Mr. Kalergis served on the board of directors and audit committee of Virginia National Bank. Mr. Kalergis received a B.A. in psychology, as well as an M.B.A. and J.D., from the University of Virginia, and is a graduate of the Harvard Business School's Leadership and Strategy in the Pharmaceutical and Biotechnology Industry program.

The Board believes Mr. Kalergis' perspective and experience as the Chief Executive Officer and a director of Diffusion, as well as his depth of operating and senior management experience in our industry and educational background, provide him with the qualifications to serve as a director.

John L. Gainer, Ph.D. – Dr. Gainer has served as a director and as our Chief Scientific Officer since January 2016. Dr. Gainer, along with Mr. Kalergis, is the Company's co-founder and served as one of Diffusions LLC's directors and as its Chief Scientific Officer from its inception in 2001 through January 2016. From 1966 until his retirement in 2005, Dr. Gainer was a professor of chemical engineering at the University of Virginia. During his career, Dr. Gainer authored more than 100 scientific journal articles, including more than 30 published in medical journals, and spent two sabbaticals investigating drug actions and related research at Karolinska Institute in Stockholm and the laboratory of a major pharmaceutical company. He has been a member of the International Society for Oxygen Transport in Tissues since its inception in 1973. Dr. Gainer received a BSChE from West Virginia University, a MS in chemical engineering from the Massachusetts Institute of Technology, and a Ph.D. in chemical engineering from the University of Delaware.

The Board believes Dr. Gainer’s perspective and experience as a director and officer of Diffusion, as well as the depth and breadth of his scientific knowledge, provide him with the qualifications to serve as a director.

Robert Adams – Mr. Adams has served as a director since January 2016 and as a director of Diffusion LLC from 2002 to January 2016. Prior to his retirement in 2015, Mr. Adams was a partner in the intellectual property law firm of Nixon & Vanderhuy P.C, where he had practiced for over 25 years, focusing on patent litigation and international patent licensing and negotiations. During that time period, Mr. Adams was lead litigation counsel in more than 50 major intellectual property lawsuits, where he directly handled, for example, all intellectual property valuations and settlements on behalf of his U.S. and foreign clients. Moreover, Mr. Adams served as the head negotiator for a well-known Japanese consumer products company for 15 years in various complicated licensing situations. Those negotiations typically involved the cross-licensing of up to hundreds of U.S. and foreign patent rights. His lead licensing activities on behalf of that client included, among other things, multi-year negotiations with Texas Instruments, Advanced Micro Devices and Freescale. Mr. Adams received a B.A. from the University of Maryland and a J.D. from George Washington University (with honors), and is a member of the Virginia State Bar.

The Board believes Mr. Adams’ perspective and experience as a director of Diffusion, as well as the depth and breadth of his intellectual property experience, provide him with the qualifications to serve as a director.

Mark T. Giles – - Mr. Giles has served as a director since January 2016 and as a director of Diffusion LLC from 2008 through January 2016. Since 2007, Mr. Giles has been the sole managing member of Panda Holdings, LLC, and since 2015, he also has been a general partner of Anchormarck Holdings, LLC; both of which engage in the investment and management of private capital. Previously, Mr. Giles served as the Chief Executive Officer of Virginia National Bank from July 1998 until June 2007 and thereafter continued to serve as the non-executive Chairman until December 2011. Prior to joining Virginia National Bank, Mr. Giles served as the president of two publicly traded bank holding companies and subsidiary banks in Texas and practiced law with the banking group of a Houston law firm. He chairs the board of Expedition Trust Company and serves on the board of the Computers4Kids Program. Mr. Giles received a B.S. from the McIntire School of Commerce at the University of Virginia and a J.D. from the University of Virginia School of Law.

The Board believes Mr. Giles’ perspective and experience as a director of Diffusion, as well as the depth and breadth of his business and legal experience, provide him with the qualifications to serve as a director.

Alan Levin – Mr. Levin has served as a director since January 2016 and as a director of Diffusion LLC from June 2015 through January 2016. He previously served as Executive Vice President and Chief Financial Officer of Endo Health Solutions Inc. (“Endo”), a global specialty healthcare company, from June 2009 until his retirement in September 2013. Prior to joining Endo, Mr. Levin worked with Texas Pacific Group, a leading private equity firm, and one of their start-up investments. Before that, he was Senior Vice President & Chief Financial Officer of Pfizer, Inc. where he worked for 20 years in a variety of executive positions of increasing responsibility, including Treasurer and Senior Vice President of Finance & Strategic Management for the company’s research and development organization. Mr. Levin received a bachelor’s degree from Princeton University and a master’s degree from New York University’s Stern School of Business. Mr. Levin is a certified public accountant. He is a member of the board of directors of Aceto Corp, a NASDAQ-traded company specialized in generics and pharmaceutical intermediate products. He is also a member of the Advisory Board of Auvon Therapeutics, a private equity fund; and the Critical Path Institute, a nonprofit collaboration between the Food and Drug Administration and pharmaceutical industry participants focused on streamlining and accelerating the development and regulatory pathways for innovative medicines.

The Board believes that the combination of Mr. Levin’s perspective and experience as a director of Diffusion; his experience in financial reporting, treasury and corporate finance (including his prior positions as chief financial officer of Endo and Pfizer, Inc.); and his executive-level experience in the pharmaceutical industry all provide him with the qualifications and skills to serve as a director.

Executive Officers

The table below sets forth, as of March 19, 2019, certain information concerning our executive officers. Biographical information for Mr. Kalergis and Dr. Gainer is included above under the heading, “— Directors .”

Name	Age	Position with Diffusion
David G. Kalergis	70	Chairman and Chief Executive Officer
John L. Gainer, Ph. D.	80	Chief Scientific Officer
William Hornung	50	Chief Financial Officer
Thomas Byrne	62	General Counsel
David R. Jones, M.D.	55	Chief Medical Officer

William K. Hornung – Mr. Hornung serves as our Chief Financial Officer, a position he has held since September 2018. Prior to this, Mr. Hornung served as the Chief Business Officer at Diffusion from July 2017 through September 2018. Previously, Mr. Hornung served as Chief Financial Officer of Contravir Pharmaceuticals from June 2014 to November 2015 and helped the company up-list to NASDAQ and raise nearly \$30 million. Prior to Contravir, from 2002 through 2014 Mr. Hornung held positions of increasing responsibility with PTC Therapeutics, most recently serving as Vice President of Finance from April 2012 to March 2014. While at PTC Therapeutics he oversaw the IPO process and raised more than \$1 billion. From 1998 through 2002 Mr. Hornung was with Elan Pharmaceuticals (formerly The Liposome Company) in various financial roles. At Liposome and Elan he was responsible for strategic planning and operations of the company's UK-based European headquarters. Earlier in his career Mr. Hornung worked for a clinical research organization where he was responsible for project management and nearly all financial aspects of the company. Mr. Hornung holds a Bachelor of Science in Accounting from the William Paterson State University of New Jersey.

Thomas Byrne – Mr. Byrne was appointed as our General Counsel in January 2016. Mr. Byrne served as a director of Diffusion LLC from 2001 to January 2016, as a director of the Company from January 2016 until April 2016 and served as Diffusion LLC's Secretary and Director of Patent Strategy from 2007 until January 2016. Prior to joining Diffusion LLC, Mr. Byrne served in in-house counsel positions at both Genentech Inc. and Amgen Inc., where he co-invented the erythropoiesis stimulating agent darbepoietin alpha (Aranesp®). From 1992 to 2000, he was a partner in the intellectual property law firm of Nixon and Vanderhye P.C. Mr. Byrne also currently acts as a consultant for start-up biotechnology companies on intellectual property, contract and business issues. He received a B.S. in chemical engineering and nuclear engineering, as well as a J.D., from the University of Virginia, and an M.S. in biochemical engineering from Yale University.

David R. Jones, M.D. - Dr. Jones serves as our Senior Medical Advisor. Dr. Jones was appointed Chief Medical Officer of the Company in January 2016, and served as such until his title was changed in January 2019, in response to policy changes at his employer, Memorial Sloan-Kettering Cancer Center in New York, NY. He served as Diffusion LLC's Chief Medical Officer from September 2012 through January 2016. In addition to serving as the Company's Senior Medical Advisor, Dr. Jones is also the Fiona and Stanley Druckenmiller Endowed Professor for Lung Cancer Research and Chief of Thoracic Surgery at Memorial Sloan-Kettering Cancer Center, a position he has held since 2013. From 2007 to 2013, Dr. Jones was Professor of Surgery and Division Chief of Thoracic & Cardiovascular Surgery at the University of Virginia. In addition to his clinical practice, Dr. Jones has published more than 220 scientific articles, authored or co-authored over 35 book chapters, and served as Principal Investigator or Co-Investigator of over 30 clinical trials. Dr. Jones received an undergraduate degree in chemistry and an M.D. from West Virginia University, and completed his thoracic surgery residency and postdoctoral research fellowship in molecular oncology at the University of North Carolina - Chapel Hill.

No family relationships exist among any of our directors or executive officers.

Section 16(a) Beneficial Ownership Reporting Compliance

Section 16(a) of the Securities Exchange Act of 1934, as amended, requires our directors and executive officers and all persons who beneficially own more than 10 percent of the outstanding shares of our common stock to file with the SEC initial reports of ownership and reports of changes in ownership of our common stock. Directors, executive officers and greater than 10 percent beneficial owners also are required to furnish us with copies of all Section 16(a) forms they file.

To our knowledge, based on a review of the copies of such reports and amendments to such reports furnished to us with respect to the year ended December 31, 2018, and based on written representations by our directors and executive officers, all required Section 16 reports under the Exchange Act, for our directors, executive officers and beneficial owners of greater than 10 percent of our common stock were filed on a timely basis during the year ended December 31, 2018.

The Board, Its Committees and Corporate Governance

Our common stock is currently listed for quotation on the NASDAQ Capital Market under the symbol “DFFN.” As required by the Listing Rules of The NASDAQ Stock Market, the Board has adopted certain governance standards, including its standard of independence.

Corporate Governance Guidelines

Our Board of Directors has adopted Corporate Governance Guidelines, a copy of which can be found on the Investor Relations—Corporate Governance section of our corporate website at www.diffusionpharma.com. Among the topics addressed in our Corporate Governance Guidelines are:

- Board size, composition and qualifications;
- Selection of directors;
- Board leadership;
- Board committees;
- Board and committee meetings;
- Executive sessions of outside directors;
- Meeting attendance by directors and non-directors;
- Appropriate information and access;
- Ability to retain advisers;
- Board interaction with corporate constituencies
- Stock ownership by directors and executive officers;
- Retirement and term limits;
- Retirement and resignation policy
- Board compensation
- Loans to directors and officers;
- Chief Executive Officer evaluation;
- Board and committee evaluations;
- Director continuing education;
- Succession planning;
- Related person transactions;
- Communication with directors;
- Director attendance at annual meetings and stockholders; and
- Change of principal occupation and board memberships

Director Independence

The Board has determined that three of our five current directors — Robert Adams, Mark T. Giles and Alan Levin — are “independent directors” under the Listing Rules of The NASDAQ Stock Market. The Listing Rules of The NASDAQ Stock Market provide a non-exclusive list of persons who are not considered independent. For example, under these rules, a director who is, or during the past three years was, employed by Diffusion or by any parent or subsidiary of Diffusion, other than prior employment as an interim chairman or Chief Executive Officer, would not be considered independent. No director qualifies as independent unless the Board affirmatively determines that the director does not have a material relationship with the listed company that would interfere with the exercise of independent judgment. In making an affirmative determination that a director is an “independent director,” the Board reviewed and discussed information provided by these individuals and by us with regard to each of their business and personal activities as they may relate to us and our management. Mr. Kalergis and Dr. Gainer are not considered independent due to their executive officer positions with the Company.

Board Leadership Structure

The Board believes that our stockholders are best served if the Board retains the flexibility to adapt its leadership structure to applicable facts and circumstances, which necessarily change over time. Accordingly, under our Corporate Governance Guidelines, the office of Chairman of the Board and Chief Executive Officer may or may not be held by one person. The Board believes it is best not to have a fixed policy on this issue and that it should be free to make this determination based on what it believes is best under the circumstances.

Currently, David G. Kalergis serves as both the Chairman of the Board and as our Chief Executive Officer. The Board believes that it is currently in the best interests of the Company's stockholders to combine these offices as it promotes information flow between management and the Board, effective decision making and an alignment of corporate strategy. However, the Board strongly endorses the concept of an independent director being in a position of leadership for the rest of the outside directors. Under our Corporate Governance Guidelines, if at any time the Chief Executive Officer and Chairman of the Board positions are held by the same person, the Board, upon recommendation of the Nominating and Corporate Governance Committee, will elect an independent director as a lead independent director. Mark T. Giles currently serves as our lead independent director.

Executive Sessions

At each regular meeting of the Board, our independent directors meet in executive session with no company management present during a portion of the meeting. Mr. Giles as our lead independent director presides over these executive sessions and serves as a liaison between the independent directors and our Chief Executive Officer.

Board Meetings and Attendance

The Board held 6 meetings during 2018. Each of the directors on the Board during 2018 attended 75 percent or more of the aggregate meetings of the Board and all committees on which he served for the period during 2018 in which he served as a director. In addition, the Company's directors are expected to attend annual meetings of stockholders, and all of the Company's directors who were serving as directors at the time of the 2018 annual meeting attended the 2018 annual meeting of stockholders or participated telephonically.

Board Committees

The Board has three standing committees: Audit Committee, Compensation Committee and Nominating and Corporate Governance Committee. Each of these committees has the composition and responsibilities described below. The Board from time to time may establish other committees to facilitate the management of our company and may change the composition and the responsibilities of our existing committees. Each of our three standing committees has a charter which can be found on the Investor Relations—Corporate Governance section of our corporate website at www.diffusionpharma.com. Messrs. Adams, Giles and Levin currently serve as the members of all three of our standing committees. Mr. Adams is the chairman of the Compensation Committee, Mr. Giles is the chairman of the Nominating and Corporate Governance Committee and Mr. Levin is the chairman of the Audit Committee.

Audit Committee

Responsibilities . The primary responsibilities of the Audit Committee include:

- overseeing our accounting and financial reporting processes, systems of internal control over financial reporting and disclosure controls and procedures on behalf of the Board and reporting the results or findings of its oversight activities to the Board;
- having sole authority to appoint, retain and oversee the work of our independent registered public accounting firm and establishing the compensation to be paid to the independent registered public accounting firm;

- establishing procedures for the receipt, retention and treatment of complaints regarding accounting, internal accounting controls and/or auditing matters and for the confidential, anonymous submission by our employees of concerns regarding questionable accounting or auditing matters;
- reviewing and pre-approving all audit services and permissible non-audit services to be performed for us by our independent registered public accounting firm as provided under the federal securities laws and rules and regulations of the SEC; and
- overseeing our system to monitor and manage risk, and legal and ethical compliance programs, including the establishment and administration (including the grant of any waiver from) a written code of ethics applicable to each of our principal executive officer, principal financial officer, principal accounting officer or controller or persons performing similar functions.

The Audit Committee has the authority to engage the services of outside experts and advisers as it deems necessary or appropriate to carry out its duties and responsibilities.

Composition and Audit Committee Financial Expert . The current members of the Audit Committee are Messrs. Adams, Giles and Levin. Mr. Levin is the chair of the Audit Committee.

Each current member of the Audit Committee qualifies as “independent” for purposes of membership on audit committees under the Listing Rules of The NASDAQ Stock Market and the rules and regulations of the SEC and is “financially literate” under the Listing Rules of The NASDAQ Stock Market. In addition, the Board has determined that Mr. Levin qualifies as an “audit committee financial expert” as defined by the rules and regulations of the SEC and meets the qualifications of “financial sophistication” under the Listing Rules of The NASDAQ Stock Market as a result of his experience in senior financial positions. Stockholders should understand that these designations related to the Audit Committee members’ experience and understanding with respect to certain accounting and auditing matters are disclosure requirements of the SEC and The NASDAQ Stock Market and do not impose upon any of them any duties, obligations or liabilities that are greater than those generally imposed on a member of the Audit Committee or of the Board.

Meetings . The Audit Committee met 4 times during 2018.

Processes and Procedures for Complaints. The Audit Committee has established procedures for the receipt, retention and treatment of complaints received by us regarding accounting, internal accounting controls, or auditing matters, and the submission by our employees, on a confidential and anonymous basis, of concerns regarding questionable accounting or auditing matters. Our personnel with such concerns are encouraged to discuss their concerns with their supervisor first, who in turn will be responsible for informing our Chief Executive Officer of any concerns raised. If an employee prefers not to discuss a particular matter with his or her own supervisor, the employee may instead discuss such matter with our Chief Executive Officer. If an individual prefers not to discuss a matter with the Chief Executive Officer or if the Chief Executive Officer is unavailable and the matter is urgent, the individual is encouraged to contact the Chair of the Audit Committee, Alan Levin.

Compensation Committee

Responsibilities . The primary responsibilities of the Compensation Committee include:

- determining the annual salaries, incentive compensation, long-term incentive compensation, special or supplemental benefits or perquisites and any and all other compensation applicable to our Chief Executive Officer and other executive officers;
- determining any revisions to corporate goals and objectives with respect to compensation for our Chief Executive Officer and other executive officers and establishing and leading a process for the full Board to evaluate the performance of our Chief Executive Officer and other executive officers in light of those goals and objectives;
- administering our equity-based compensation plans, including determining specific grants of options and other awards for executive officers and other employees under our equity-based compensation plans;

- reviewing and discussing with our Chief Executive Officer and reporting periodically to the Board plans for executive officer development and corporate succession plans for the Chief Executive Officer and other key executive officers and employees; and
- establishing and leading a process for determining of the compensation applicable to the non-employee directors on the Board.

The Compensation Committee has the authority to engage the services of outside experts and advisers as it deems necessary or appropriate to carry out its duties and responsibilities.

Composition . The current members of the Compensation Committee are Messrs. Adams, Giles and Levin. Mr. Adams is the chair of the Compensation Committee. Each of the three current members of the Compensation Committee is an “independent director” under the Listing Rules of The NASDAQ Stock Market and a “non-employee director” within the meaning of Rule 16b-3 under the Exchange Act.

Meetings . The Compensation Committee met 10 times during 2018.

Processes and Procedures for Consideration and Determination of Executive Compensation . As mentioned above, the Compensation Committee has authority to determine all compensation applicable to our executive officers. In setting executive compensation for our executive officers, the Compensation Committee considers, among other things, the following primary factors: each executive’s position within the company and the level of responsibility; the ability of the executive to affect key business initiatives; the executive’s individual experience and qualifications; compensation paid to executives of comparable positions by companies similar to our company; company and individual performance; the executive’s current and historical compensation levels; and input from the Compensation Committee’s independent consulting firm, Radford (“Radford”).

In making decisions regarding the form and amount of compensation to be paid to our executive officers (other than our Chief Executive Officer), the Compensation Committee considers and gives weight to the recommendations of our Chief Executive Officer recognizing that due to his reporting and otherwise close relationship with each executive, the Chief Executive Officer often is in a better position than the Compensation Committee to evaluate the performance of each executive (other than himself). In making decisions regarding the form and amount of compensation to be paid to our Chief Executive Officer, the Compensation Committee considers the recommendation of the Chief Executive Officer with respect to his own compensation and the Compensation Committee’s own assessment of the Chief Executive Officer’s annual performance and input from other Board members. The Compensation Committee meets in executive session regularly and makes all executive compensation decisions without the presence of the Chief Executive Officer or any executive or employee of our company.

The Compensation Committee has retained the services of Radford to provide advice with respect to executive compensation. Radford was engaged directly by the Compensation Committee in 2017 and 2018 and did not advise our management and only worked with management with the express permission of the Compensation Committee. Radford did not provide any services to our company in 2017 or 2018 other than those for which it was retained by the Compensation Committee. Radford’s engagement by the Compensation Committee includes reviewing and advising on all significant aspects of executive compensation. This includes base salaries, short-term cash incentives and long-term equity incentives for our executives, and cash compensation and long-term equity incentives for our non-employee directors. In so doing, at the request of the Compensation Committee, Radford recommended a peer group of companies, collected relevant market data from these companies to allow the Compensation Committee to compare elements of our executive compensation program to those of our peers and made other recommendations to the Compensation Committee regarding certain aspects of our executive compensation program. In making decisions regarding the form and amount of compensation to be paid to our executives, the Compensation Committee considers the information gathered by, and the recommendations of, Radford.

Processes and Procedures for Consideration and Determination of Director Compensation . The Board has delegated to the Compensation Committee the responsibility, among other things, to establish and lead a process for determining compensation payable to our non-employee directors. The Compensation Committee makes recommendations regarding compensation payable to our non-employee directors to the entire Board, which then makes the final decision.

In making decisions regarding compensation to be paid to our non-employee directors, the Board considers the recommendations of Radford, but also other factors, such as its own views as to the form and amount of compensation to be paid, the current and anticipated time demands placed on non-employee directors and other factors that may be relevant.

Nominating and Corporate Governance Committee

Responsibilities . The primary responsibilities of the Nominating and Corporate Governance Committee are:

- identifying individuals qualified to become Board members;
- recommending director nominees for each annual meeting of our stockholders and director nominees to fill any vacancies that may occur between meetings of stockholders;
- being aware of best practices in corporate governance and developing and recommending to the Board a set of corporate governance standards to govern the Board, its committees, our company and our employees in the conduct of our business and affairs; and
- developing and overseeing a Board and Board committee evaluation process.

The Nominating and Corporate Governance Committee has the authority to engage the services of outside experts and advisers as it deems necessary or appropriate to carry out its duties and responsibilities.

Composition . The current members of the Nominating and Corporate Governance Committee are Messrs. Adams, Giles and Levin. Mr. Giles is the chair of the Nominating and Corporate Governance Committee. Each of the three current members of the Nominating and Corporate Governance Committee is an “independent director” within the meaning of the Listing Rules of The NASDAQ Stock Market.

Meetings . The Nominating and Corporate Governance Committee met 6 times during 2018.

Director Nominations Process

In selecting nominees for the Board, the Nominating and Corporate Governance Committee first determines whether the incumbent directors are qualified to serve, and wish to continue to serve, on the Board. The Nominating and Corporate Governance Committee believes that our company and stockholders benefit from the continued service of qualified incumbent directors because those directors have familiarity with and insight into our company’s affairs that they have accumulated during their tenure with Diffusion. Appropriate continuity of Board membership also contributes to the Board’s ability to work as a collective body. Accordingly, it is the practice of the Nominating and Corporate Governance Committee, in general, to re-nominate an incumbent director at the upcoming annual meeting of stockholders if the director wishes to continue his or her service with the Board, the director continues to satisfy the Nominating and Corporate Governance Committee’s criteria for membership on the Board, the Nominating and Corporate Governance Committee believes the director continues to make important contributions to the Board and there are no special, countervailing considerations against re-nomination of the director.

In identifying and evaluating new candidates for election to the Board, the Nominating and Corporate Governance Committee intends to first solicit recommendations for nominees from persons whom the Nominating and Corporate Governance Committee believes are likely to be familiar qualified candidates having the qualifications, skills and characteristics required for Board nominees from time to time. Such persons may include members of the Board and senior management of Diffusion. In addition, the Nominating and Corporate Governance Committee may engage a search firm to assist it in identifying qualified candidates. The Nominating and Corporate Governance Committee then intends to review and evaluate each candidate whom it believes merits serious consideration, taking into account available information concerning the candidate, any qualifications or criteria for Board membership established by the Nominating and Corporate Governance Committee, the existing composition of the Board and other factors that it deems relevant. In conducting its review and evaluation, the Nominating and Corporate Governance Committee may solicit the views of our management, other Board members and any other individuals it believes may have insight into a candidate. The Nominating and Corporate Governance Committee may designate one or more of its members and/or other Board members to interview any proposed candidate.

The Nominating and Corporate Governance Committee will consider recommendations for the nomination of directors submitted by our stockholders. The Nominating and Corporate Governance Committee will evaluate candidates recommended by stockholders in the same manner as those recommended as stated above.

There are no formal requirements or minimum qualifications that a candidate must meet in order for the Nominating and Corporate Governance Committee to recommend the candidate to the Board. The Nominating and Corporate Governance Committee believes that each nominee should be evaluated based on his or her merits as an individual, taking into account the needs of the Company and the Board. However, in evaluating candidates, there are a number of criteria that the Nominating and Corporate Governance Committee generally views as relevant and is likely to consider. Some of these factors include:

- whether the candidate is an “independent director” under applicable independence tests under the federal securities laws and rules and regulations of the SEC;
- whether the candidate is “financially sophisticated” and otherwise meets the requirements for serving as a member of an audit committee;
- whether the candidate is an “audit committee financial expert” under the rules and regulations of the SEC;
- the needs of the Company with respect to the particular talents and experience of our directors;
- the personal and professional integrity and reputation of the candidate;
- the candidate’s level of education and business experience;
- the candidate’s business acumen;
- the candidate’s level of understanding of our business and industry and other industries relevant to our business;
- the candidate’s ability and willingness to devote adequate time to the work of the Board and its committees;
- the fit of the candidate’s skills and personality with those of other directors and potential directors in building a board of directors that is effective, collegial and responsive to the needs of our company;
- whether the candidate possesses strategic thinking and a willingness to share ideas;
- the candidate’s diversity of experiences, expertise and background; and
- the candidate’s ability to represent the interests of all stockholders and not a particular interest group.

While we do not have a stand-alone diversity policy, in considering whether to recommend any director nominee, including candidates recommended by stockholders, the Nominating and Corporate Governance Committee will consider the factors above, including the candidate’s diversity of experiences, expertise and background. The Nominating and Corporate Governance Committee seeks nominees with a broad diversity of experience, expertise and backgrounds. The Nominating and Corporate Governance Committee does not assign specific weights to particular criteria and no particular criterion is necessarily applicable to all prospective nominees. We believe that the backgrounds and qualifications of the directors, considered as a group, should provide a significant mix of experience, knowledge and abilities that will allow the Board to fulfill its responsibilities.

Board Oversight of Risk

The Board as a whole has responsibility for risk oversight, with more in-depth reviews of certain areas of risk being conducted by the relevant Board committees that report on their deliberations to the full Board. The oversight responsibility of the Board and its committees is enabled by management reporting processes that are designed to provide information to the Board about the identification, assessment and management of critical risks and management’s risk mitigation strategies. The areas of risk that we focus on include regulatory, operational, financial (accounting, credit, liquidity and tax), legal, compensation, competitive, health, safety and environment, economic, political and reputational risks.

The standing committees of the Board oversee risks associated with their respective principal areas of focus. The Audit Committee’s role includes a particular focus on the qualitative aspects of financial reporting to stockholders, on our processes for the management of business and financial risk, our financial reporting obligations and for compliance with significant applicable legal, ethical and regulatory requirements. The Audit Committee, along with management, is also responsible for developing and participating in a process for review of important financial and operating topics that present potential significant risk to our company. The Compensation Committee is responsible for overseeing risks and exposures associated with our compensation programs and arrangements, including our executive and director compensation programs and arrangements, and management succession planning. The Nominating and Corporate Governance Committee oversees risks relating to our corporate governance matters and policies and director succession planning.

We recognize that a fundamental part of risk management is understanding not only the risks a company faces and what steps management is taking to manage those risks, but also understanding what level of risk is appropriate for our company. The involvement of the full Board in setting our business strategy is a key part of the Board's assessment of management's appetite for risk and also a determination of what constitutes an appropriate level of risk for our company.

We believe our current Board leadership structure is appropriate and helps ensure proper risk oversight for our company for a number of reasons, including: (1) general risk oversight by the full Board in connection with its role in reviewing our key long-term and short-term business strategies and monitoring on an on-going basis the implementation of our key business strategies; (2) more detailed oversight by our standing Board committees that are currently comprised of and chaired by our independent directors and (3) the focus of our Chairman of the Board on allocating appropriate Board agenda time for discussion regarding the implementation of our key business strategies and specifically risk management.

Code of Business Conduct and Ethics

Our Code of Business Conduct and Ethics applies to all of our directors, executive officers and other employees, and meets the requirements of the SEC. A copy of our Code of Business Conduct and Ethics is available on the Investor Relations—Corporate Governance—Code of Business Conduct and Ethics section of our corporate website at www.diffusionpharma.com.

Process Regarding Stockholder Communications with Board of Directors

Stockholders may communicate with the Board or any one particular director by sending correspondence, addressed to our Secretary, Diffusion Pharmaceuticals Inc., 1317 Carlton Avenue, Suite 200, Charlottesville, Virginia 22902, with an instruction to forward the communication to the Board or one or more particular directors. Our Secretary will forward promptly all such stockholder communications to the Board of Directors or the one or more particular directors, with the exception of any advertisements, solicitations for periodical or other subscriptions and other similar communications.

ITEM 11. EXECUTIVE COMPENSATION

Summary Compensation Table

The table below provides summary compensation information concerning compensation awarded to the individuals that served as our named executive officers for the years ended December 31, 2018 and December 31, 2017 (as applicable).

SUMMARY COMPENSATION TABLE

Name and Principal Position	Year	Salary ⁽¹⁾	Non-Equity Incentive Plan Compensation ⁽²⁾	Option awards ⁽³⁾	All other compensation ⁽⁴⁾	Total
David G. Kalergis	2018	\$ 439,192	\$ 66,208	\$ 64,905	\$ 16,836	\$ 587,141
<i>Chief Executive Officer</i>	2017	\$ 317,945	\$ 81,000	\$ 99,966	\$ 11,613	\$ 510,524
John L. Gainer, Ph.D.	2018	\$ 369,896	\$ 69,473	\$ 53,100	\$ 14,568	\$ 507,037
<i>Chief Scientific Officer</i>	2017	\$ 265,958	\$ 89,000	\$ 82,899	\$ 10,508	\$ 448,365
William K. Hornung ⁽⁵⁾	2018	\$ 214,583	\$ 49,429	\$ 106,200	\$ 1,250	\$ 371,462
<i>Chief Financial Officer</i>	2017	\$ 70,087	\$ 60,000	\$ —	\$ —	\$ 130,087
Ben L. Shealy	2018	\$ 175,253	\$ —	\$ 29,505	\$ 203,428	\$ 408,186
<i>Former Senior Vice President - Finance, Treasurer & Secretary</i>	2017	\$ 178,400	\$ 51,000	\$ 56,323	\$ 4,312	\$ 290,035

⁽¹⁾ All of the 2018 and 2017 base salaries for Messrs. Kalergis, Hornung and Shealy and Dr. Gainer were paid in cash.

⁽²⁾ Represents the annual cash incentive bonuses earned by our named executive officers in respect of 2018 and 2017 (as applicable), as described further below under “-2018 Bonus Compensation.

⁽³⁾ The amounts shown in this column reflect the grant date fair value of option awards granted during the applicable year, calculated in accordance with the provisions of ASC Topic 718 and determined without regard to forfeitures. The assumptions used in the Black-Scholes model for the fiscal years ended December 31, 2018 and 2017 are disclosed elsewhere in this filing.

⁽⁴⁾ The amounts reported in this column represent 401(k) Plan matching contributions by the Company for the applicable year. The amounts reported in this column for Mr. Shealy represent, in addition to the 401(k) matching contributions of \$7,101, the total severance benefits paid or payable to him \$196,327 as a result of his termination of employment with the Company, effective as of September 21, 2018, as described in more detail under “- *Post-Termination Severance and Change in Control Arrangements.*”

⁽⁵⁾ Mr. Hornung began his employment with the Company on August 30, 2017 as the Chief Business Officer, a title he held until September 21, 2018, on which date he assumed the role of Chief Financial Officer. The total amount of his salary disclosed in the table above reflects both the salary he earned in 2018 as the Chief Business Officer (through September 20, 2018) and the salary he earning in 2018 as the Chief Financial Officer (on and after September 21, 2018).

Employment Agreements

David G. Kalergis, Chief Executive Officer . Effective September 6, 2016, we entered into an employment agreement with David G. Kalergis pursuant to which he serves as our Chief Executive Officer. The employment agreement has an indefinite term. Mr. Kalergis is currently entitled to an annual base salary of \$439,192 (representing an increase from his annual base salary of \$410,000 as of the date of his employment agreement), subject to increase at the discretion of the Board. Mr. Kalergis has the opportunity to earn a target annual bonus of 45 percent of his base salary. The Board may, in its discretion, pay a portion of Mr. Kalergis' annual salary and annual bonus in the form of equity or equity-based compensation, provided that commencing with the year following the year in which a "change of control" (as defined in the employment agreement) occurs, Mr. Kalergis' entire base salary and annual bonus will be paid in cash. For 2018, Mr. Kalergis' entire base salary was paid in cash. The employment agreement contains certain severance and change of control provisions as described in more detail under the heading "*— Post-Termination Severance and Change in Control Arrangements* ." The employment agreement also contains certain non-competition and non-solicitation provisions (each applicable during employment and for 24 months thereafter), as well as confidentiality and non-disparagement provisions (each applicable during employment and at all times thereafter).

John L. Gainer, Chief Scientific Officer. Effective October 18, 2016, we entered into an employment agreement with John L. Gainer pursuant to which he serves as our Chief Scientific Officer. The employment agreement has an indefinite term. Dr. Gainer is currently entitled to an annual base salary of \$369,896 (representing an increase from his annual base salary of \$340,000 as of the date of his employment agreement), subject to increase at the discretion of the Board. Dr. Gainer has the opportunity to earn a target annual bonus of 35 percent of his base salary. The Board may, in its discretion, pay a portion of Dr. Gainer's annual salary and annual bonus in the form of equity or equity-based compensation, provided that commencing with the year following the year in which a "change of control" (as defined in the employment agreement) occurs, Dr. Gainer's entire base salary and annual bonus will be paid in cash. For 2018, Dr. Gainer's entire base salary was paid in cash. The employment agreement contains certain severance and change of control provisions as described in more detail under the heading "*— Post-Termination Severance and Change in Control Arrangements* ." The employment agreement also contains certain non-competition and non-solicitation provisions (each applicable during employment and for 18 months thereafter), as well as confidentiality and non-disparagement provisions (each applicable during employment and at all times thereafter).

William K. Hornung, Chief Financial Officer. Effective September 21, 2018, we entered into an amended and restated employment agreement with William Hornung pursuant to which he serves as our Chief Financial Officer. The employment agreement has an indefinite term. Mr. Hornung is entitled to an annual base salary of \$298,100, subject to increase at the discretion of the Board. Mr. Hornung has the opportunity to earn a target annual bonus of 35 percent of his base salary. The Board may, in its discretion, pay a portion of Mr. Hornung's annual salary and annual bonus in the form of equity or equity-based compensation, provided that commencing with the year following the year in which a "change of control" (as defined in the employment agreement) occurs, Mr. Hornung's entire base salary and annual bonus will be paid in cash. For 2018, the cash portion of Mr. Hornung's base salary was \$216,666. The employment agreement contains certain severance and change of control provisions as described in more detail under the heading "*— Post-Termination Severance and Change in Control Arrangements* ." The employment agreement also contains certain non-competition and non-solicitation provisions (each applicable during employment and for 18 months thereafter), as well as confidentiality and non-disparagement provisions (each applicable during employment and at all times thereafter).

Ben L. Shealy , Former Senior Vice President - Finance, Treasurer and Secretary . Effective October 12, 2016, we entered into an employment agreement with Ben L. Shealy pursuant to which he served as our Senior Vice President - Finance, Treasurer and Secretary. The employment agreement had an indefinite term. Mr. Shealy was entitled to an annual base salary of \$231,000, subject to increase at the discretion of the Board. Mr. Shealy had the opportunity to earn a target annual bonus of 25 percent of his base salary. The Board may, in its discretion, pay a portion of Mr. Shealy's annual salary and annual bonus in the form of equity or equity-based compensation, provided that commencing with the year following the year in which a "change of control" (as defined in the employment agreement) occurs, Mr. Shealy's entire base salary and annual bonus would have been paid in cash. For 2018, Mr. Shealy's entire base salary was paid in cash. The employment agreement contained certain severance and change of control provisions as described in more detail under the heading "*-Post-Termination Severance and Change in Control Arrangements.*" The employment agreement also contained certain non-competition and non-solicitation provisions (each applicable during employment and for 18 months thereafter), as well as confidentiality and non-disparagement provisions (each applicable during employment and at all times thereafter).

On September 21, 2018, Mr. Shealy's employment with the Company ended. In connection with his cessation of employment, the Company and Mr. Shealy entered into a separation agreement memorializing his severance benefits and providing for certain modifications to the vesting and termination provision of Mr. Shealy's existing equity awards, all as described in more detail below under the heading “- *Post-Termination Severance and Change in Control Arrangements* .”

2018 Equity Awards

The Compensation Committee administers the Company's 2015 Equity Incentive Plan, as amended, pursuant to which the Company may grant stock options and other equity or equity-based awards to our named executive officers from time to time. The option grants made in 2018 to the named executive officers vest and become exercisable in equal parts each month until fully vested on the third anniversary of the grant date, subject to their continued employment through the applicable vesting date.

2018 Bonus Compensation

Executive bonuses are determined by the Compensation Committee. The Compensation Committee determines whether bonuses are earned and the amounts of the bonus payout by considering a number of factors, the principal factor being based upon the performance goals developed by the Compensation Committee. Other important factors include clinical trial progress, business development activities, status of public filings and stock price performance.

Outstanding Equity Awards at Fiscal Year End

The table below provides information regarding unexercised stock option awards held by each of our named executive officers that remained outstanding at December 31, 2018. None of our named executive officers held any other stock awards on December 31, 2018.

Name	Grant Date	Option Awards			
		Number of Securities Underlying Unexercised Options (#) Exercisable	Number of Securities Underlying Unexercised Options (#) Unexercisable ⁽¹⁾	Option Exercise Price (\$)	Option Expiration Date
David G. Kalergis	5/17/2012	1,973	—	\$ 31.50	5/17/2022
	10/9/2012	609	—	\$ 31.50	10/9/2022
	10/9/2012	1,827	—	\$ 31.50	10/9/2022
	10/5/2013	853	—	\$ 51.00	10/5/2023
	10/5/2013	1,218	—	\$ 91.50	10/5/2023
	12/1/2014	1,218	—	\$ 61.50	12/1/2024
	12/1/2014	853	—	\$ 61.50	12/1/2024
	10/30/2015	2,436	—	\$ 81.00	10/30/2025
	10/30/2015	2,211	—	\$ 81.00	10/30/2015
	5/16/2016	1,177	185	\$ 144.00	5/16/2026
	12/8/2016	4,866	2,134	\$ 41.10	12/8/2026
	5/10/2017	1,520	1,214	\$ 44.40	5/10/2027
	1/2/2018	1,224	2,443	\$ 17.70	1/2/2028
	John L. Gainer, Ph.D.	5/17/2012	1,510	—	\$ 31.50
10/9/2012		609	—	\$ 31.50	10/9/2022
10/9/2012		1,218	—	\$ 31.50	10/9/2022
10/5/2013		609	—	\$ 51.00	10/5/2023
10/5/2013		1,218	—	\$ 91.50	10/5/2023
12/1/2014		1,218	—	\$ 615.00	12/1/2024
10/1/2014		731	—	\$ 61.50	10/1/2024
10/30/2015		2,436	—	\$ 81.00	10/30/2025
10/30/2015		1,462	—	\$ 81.00	10/30/2025
5/16/2016		481	75	\$ 144.00	5/16/2026
12/8/2016		1,575	692	\$ 41.10	12/8/2026
5/10/2017	1,260	1,007	\$ 44.40	5/10/2027	
1/2/2018	1,008	1,992	\$ 17.70	1/2/2028	
William K. Hornung	1/2/2018	2,004	3,996	\$ 17.70	1/2/2028
Ben L. Shealy	5/17/2012	2,801	—	\$ 31.50	5/17/2022
	10/9/2012	1,340	—	\$ 31.50	10/9/2022
	10/5/2013	609	—	\$ 51.00	10/5/2023
	12/1/2014	731	—	\$ 615.00	12/1/2024
	10/30/2015	1,583	—	\$ 81.00	10/30/2025
	5/16/2016	598	80	\$ 144.00	5/16/2026
	12/8/2016	1,067	319	\$ 41.10	12/8/2026
	5/10/2017	1,540	680	\$ 44.40	5/10/2027
1/2/2018	1,667	1,104	\$ 17.70	1/2/2028	

⁽¹⁾ The unvested shares underlying each option grant are scheduled to vest in equal monthly installments over the 36 month period following the grant date (with vesting occurring on the applicable monthly anniversary of the grant date, except for the options granted on December 8, 2016 and on May 10, 2017, which vest on the last day of each month following the grant date.)

401(k) Retirement Plan

We maintain the Diffusion Pharmaceuticals Inc. 401(k) plan pursuant to which all eligible employees are entitled to make pre-tax and after-tax contributions of their compensation. In addition, the Company makes discretionary matching contributions at a rate of 100% for contributions up to 3% of the participant's eligible compensation and 50% for any additional contributions up to 5% of the participant's eligible compensation. The matching contributions received by our named executive officers in 2017 and 2018 are reported in the "All Other Compensation" column of the Summary Compensation Table above.

Post-Termination Severance and Change in Control Arrangements

Current Named Executive Officers

As described under the heading "*— Employment Agreements*," we have entered into employment agreements with each of Messrs. Kalergis and Hornung and Dr. Gainer that provide for certain severance and change of control benefits, subject to the execution and non-revocation of a release of claims by the executive or his estate (as applicable). Under Mr. Kalergis' employment agreement, if his employment is terminated by us other than for "cause," death or "disability," or by Mr. Kalergis for "good reason" (as such terms are defined in the employment agreement), Mr. Kalergis will be entitled to any unpaid bonus earned in the year prior to the termination, a pro-rata portion of the bonus earned during the year of termination, continuation of base salary for 12 months, plus 12 months of COBRA premium reimbursement, provided that if such termination occurs within 60 days before or within 24 months following a "change of control" (as defined in the employment agreement), then Mr. Kalergis will be entitled to receive the same severance benefits as provided above, except that he will receive (a) a payment equal to two times the sum of his base salary and the higher of his target annual bonus opportunity and the bonus payment he received for the year immediately preceding the year in which the termination occurred instead of 12 months of base salary continuation, and (b) a payment equal to 36 times the monthly COBRA premium for him and his eligible dependents instead of 12 months of COBRA reimbursements (the payments in clauses (a) and (b) are paid in a lump sum in some cases and partly in a lump sum and partly in installments over 12 months in other cases). In addition, if Mr. Kalergis' employment is terminated by us without cause or by Mr. Kalergis for good reason, in either case, upon or within 24 months following a change of control, then Mr. Kalergis will be entitled to full vesting of all equity awards received by him from us (with any equity awards that are subject to the satisfaction of performance goals deemed earned at not less than target performance, and with any equity award that is in the form of a stock option or stock appreciation right to remain outstanding and exercisable for 24 months following the termination date (but in no event beyond the expiration date of the applicable option or stock appreciation right)).

Under the employment agreements for Mr. Hornung and Dr. Gainer, in the event that the executive's employment is terminated by us other than for "cause", death or "disability" or upon his resignation for "good reason" (as such terms are defined in the applicable employment agreement), the executive will be entitled to any unpaid bonus earned in the year prior to the termination, a pro-rata portion of the bonus earned during the year of termination, continuation of base salary for 9 months, plus 12 months of COBRA premium reimbursement, provided that if such termination occurs within 60 days before or within 24 months following a "change of control" (as defined in the applicable employment agreement), then the executive will be entitled to receive the same severance benefits as provided above, except that he will receive (a) a payment equal to 1.5 times the sum of his base salary and the higher of his target annual bonus opportunity and the bonus payment he received for the year immediately preceding the year in which the termination occurred instead of 9 months of base salary continuation and (b) a payment equal to 18 times the monthly COBRA premium for the executive and his eligible dependents instead of 12 months of COBRA reimbursements (the payments in clauses (a) and (b) are paid in a lump sum in some cases and in installments over 9 or 12 months in other cases). In addition, if the executive's employment is terminated by the Company without cause or by the executive for good reason, in either case, upon or within 24 months following a change of control, then the executive will be entitled to full vesting of all equity awards received by the executive from us (with any equity awards that are subject to the satisfaction of performance goals deemed earned at not less than target performance, and with any equity award that is in the form of a stock option or stock appreciation right to remain outstanding and exercisable for 24 months following the termination date (but in no event beyond the expiration date of the applicable option or stock appreciation right)).

Under the employment agreements for each of Messrs. Kalergis, Hornung and Dr. Gainer, in the event that the executive’s employment is terminated due to his death or disability, he (or his estate) will be entitled to any unpaid bonus earned in the year prior to the termination, a pro-rata portion of the bonus earned during the year of termination, 12 months of COBRA premium reimbursement and accelerated vesting of (a) all equity awards received in payment of base salary or an annual bonus and (b) with respect to any other equity award, the greater of the portion of the unvested equity award that would have become vested within 12 months after the termination date had no termination occurred and the portion of the unvested equity award that is subject to accelerated vesting (if any) upon such termination under the applicable equity plan or award agreement (with performance goals deemed earned at not less than target performance, and with any equity award that is in the form of a stock option or stock appreciation right to remain outstanding and exercisable for 12 months following the termination date or, if longer, such period as provided under the applicable equity plan or award agreement (but in no event beyond the expiration date of the applicable option or stock appreciation right)).

Further, under the terms of the stock option agreements with our executives (including, for the purposes, Mr. Shealy’s outstanding stock options), upon a completion of a “change of control” (as defined in the Diffusion Pharmaceuticals Inc. 2015 Equity Incentive Plan), options held by our executives will become immediately vested and remain exercisable through their expiration date regardless of whether the holder remains in the employment or service of the Company after the change of control. Alternatively, in connection with a change of control, the Compensation Committee may, in its sole discretion, cash out the options.

Ben L. Shealy

In connection with Mr. Shealy’s termination of employment, we entered into a separation agreement with Mr. Shealy memorializing the following severance benefits payable to him: (i) a pro-rata portion of the annual bonus earned for 2018 (payable at the same time as if he had not terminated employment), (ii) continuation of base salary for 9 months and (iii) 12 months of COBRA premium reimbursement. Mr. Shealy’s separation agreement further provides for continued vesting of any unvested stock options held by him as of the separation date and continued exercisability of any stock options held by him as of the separation date that are or become vested upon or following the separation date, in each case, in accordance with the terms of the applicable option agreements as if his employment had not terminated (and in no event beyond the applicable option expiration date).

DIRECTOR COMPENSATION

Overview of Director Compensation Program

As described in more detail under the heading “*Corporate Governance—Compensation Committee—Responsibilities*,” the Board has delegated to the Compensation Committee the responsibility, among other things, to establish and lead a process for the determination of compensation payable to our non-employee directors. The Compensation Committee makes recommendations regarding compensation payable to our non-employee directors to the entire Board, which then makes final decisions regarding such compensation.

The principal elements of our director compensation program for 2018 included:

- cash compensation in the form of annual cash retainers; and
- long-term equity-based incentive compensation, in the form of stock options.

We do not compensate our employee directors, Mr. Kalergis and Dr. Gainer, separately for serving on the Board.

Cash Compensation

The cash compensation paid to the non-employee members of the Board for 2018 consisted of the following cash retainers.

Description	Annual Cash Retainer
Board Member	\$ 35,000
Lead Independent Director of the Board	\$ 3,000
Audit Committee Chair	\$ 15,000
Compensation Committee Chair	\$ 10,000
Nominating and Corporate Governance Committee Chair	\$ 7,000
Audit Committee Member (other than Chair)	\$ 7,500
Compensation Committee Member (other than Chair)	\$ 5,000
Nominating and Corporate Governance Committee Member (other than Chair)	\$ 2,500

The annual cash retainers are paid in accordance with the Company’s standard payroll practices. The Compensation Committee has also reserved the right to make a portion of such payments in the form of equity rather than cash under certain conditions. During the fiscal year 2018, all retainers were paid in cash.

Long-Term Equity-Based Incentive Compensation

In addition to cash compensation, our non-employee directors receive long-term equity-based incentive compensation in the form of options to purchase shares of our common stock. Upon a non-employee director's initial appointment to the Board, he or she shall receive a stock option award valued at \$100,000 vesting in equal annual installments over three years. In addition, each non-employee director annually receives a stock option award valued at \$50,000 vesting in equal monthly installments over one year (previously, three years), unless otherwise provided by the Compensation Committee. All such options have a ten-year term and an exercise price equal to the fair market value of our common stock on the grant date.

See note 1 to the Director Compensation Table under the heading “— *Summary Director Compensation Table for Fiscal 2018* ” for a summary of all options granted to our non-employee directors during the year ended December 31, 2018. See note 2 to the Director Compensation Table under the heading “— *Summary Director Compensation Table for Fiscal 2018* ” for a summary of all options to purchase shares of our common stock held by our non-employee directors as of December 31, 2018.

Summary Director Compensation Table for Fiscal 2018

The table below provides summary information concerning the compensation of each individual who served as a director of the Company during the year ended December 31, 2018, other than David G. Kalergis, our Chief Executive Officer, and John L. Gainer, Ph.D., our Chief Scientific Officer.

Name	Fees Earned or Paid in Cash (\$)	Option Awards (\$) (1) (2)	All Other Compensation (\$)	Total (\$)
Isaac Blech ⁽³⁾	\$ —	\$ —	\$ —	\$ —
Mark T. Giles	\$ 58,000	\$ 50,869	\$ —	\$ 108,869
Alan Levin	\$ 58,000	\$ 50,869	\$ —	\$ 108,869
Robert Adams	\$ 56,000	\$ 50,869	\$ —	\$ 106,869
Robert Ruffolo ⁽⁴⁾	\$ 56,000	\$ 50,869	\$ —	\$ 106,869

⁽¹⁾ The amounts shown in this column reflect the grant date fair value of option awards granted during 2018, calculated in accordance with the provisions of ASC Topic 718, determined without regard to forfeitures. See the assumptions used in the Black-Scholes model in the notes to the audited financial statements included elsewhere in this report.

(2) As of December 31, 2018, our non-employee directors held stock options to acquire the following number of shares of our common stock: Mr. Giles, options to acquire 14,050 shares of our common stock; Mr. Levin, options to acquire 12,757 shares of our common stock; Mr. Adams, options to acquire 15,220 shares of our common stock; and Dr. Ruffolo, options to acquire 7,805 shares of our common stock.

(3) Mr. Blech resigned from the Board effective on November 8, 2018.

(4) Mr. Ruffolo resigned from the Board effective on January 15, 2019.

ITEM 12. SECURITY OWNERSHIP OF CERTAIN BENEFICIAL OWNERS AND MANAGEMENT AND RELATED STOCKHOLDER MATTERS

Equity Compensation Plan Information

Plan Category	Number of Securities to be Issued upon Exercise of Outstanding Options, Warrants and Rights (a)	Weighted Average Exercise Price of Outstanding Options, Warrants and Rights (b)	Number of Securities Remaining Available for Future Issuance under Equity Compensation Plans (Excluding Securities Reflected in Column (a)) (c)
Equity compensation plans approved by security holders			
Equity compensation plans not approved by security holders			
Total	2,301,331		

Security Ownership of Certain Beneficial Owners and Management

Based on information available to us and filings with the SEC, the following table sets forth certain information regarding the beneficial ownership (as defined by Rule 13d-3 under the Exchange Act) of our outstanding common stock as of March 13, 2019 for (i) each of our current directors and nominees; (ii) each of our current named executive officers (as defined in Item 402(a)(3) of Regulation S-K under the Exchange Act); and (iii) all of our current directors and executive officers as a group. As of March 13, 2019, no beneficial owner owned 5% or more of the shares of common stock then outstanding.

Beneficial ownership and percentage ownership are determined in accordance with the rules of the SEC and include voting or investment power with respect to shares of stock. This information does not necessarily indicate beneficial ownership for any other purpose. Under these rules, shares of common stock issuable under stock options or warrants that are exercisable or convertible within 60 days of March 13, 2019 are deemed outstanding for the purpose of computing the beneficial ownership percentage of the holder thereof, but are not deemed outstanding for the purpose of computing the beneficial ownership percentage of any other person. Ownership is based upon information provided by each respective director and officer, Forms 3 and 4, Schedules 13D and 13G and other public documents filed with the SEC for some of the stockholders.

Unless otherwise indicated and subject to applicable community property laws, to our knowledge, each stockholder named in the following table possesses sole voting and investment power over their shares of common stock, except for those jointly owned with that person's spouse. Unless otherwise indicated below, the address of each person listed on the table is c/o Diffusion Pharmaceuticals Inc. 1317 Carlton Avenue, Suite 200, Charlottesville, Virginia 22902.

Name and Address of Beneficial Owner	Shares of Common Stock Beneficially Owned ⁽¹⁾	Percentage of Total Voting Power ⁽²⁾
<i>Current Directors and Executive Officers</i>		
David G. Kalergis ⁽³⁾ <i>Chief Executive Officer and Director</i>	31,243	*
John L. Gainer ⁽⁴⁾ <i>Chief Scientific Officer and Director</i>	40,620	1.2%
Mark T. Giles ⁽⁵⁾ <i>Director</i>	66,544	1.9%
Alan Levin ⁽⁶⁾ <i>Director</i>	13,757	*
Robert Adams ⁽⁷⁾ <i>Director</i>	16,918	*
William K. Hornung ⁽⁸⁾ <i>Chief Financial Officer</i>	4,487	*
Thomas Byrne ⁽⁹⁾ <i>General Counsel</i>	20,927	*
Ben L. Shealy ⁽¹⁰⁾ <i>Former Senior Vice President - Finance, Treasurer and Secretary</i>	10,289	*
All current directors and executive officers as a group (seven persons)	204,785	5.6%

⁽¹⁾ Represents shares of common stock held as of March 13, 2019 plus shares of common stock that may be acquired upon exercise of options, warrants and other rights exercisable within sixty (60) days of March 13, 2019.

⁽²⁾ Based on shares of common stock that were issued and outstanding as of March 13, 2019. The percentage ownership and voting power for each person (or all directors and executive officers as a group) is calculated by assuming (i) the exercise or conversion of all options, warrants and convertible securities exercisable or convertible within sixty (60) days of March 13, 2019 held by such person and (ii) the non-exercise and non-conversion of all outstanding warrants, options and convertible securities held by all other persons (including our other directors and executive officers).

⁽³⁾ Consists of (a) 4,578 shares held directly by Mr. Kalergis directly, (b) 493 shares held by Mr. Kalergis' wife, (c) 2,551 shares held jointly with Mr. Kalergis' wife and (d) 23,621 shares of common stock issuable upon the exercise of options exercisable within 60 days of March 13, 2019.

⁽⁴⁾ Consists of (a) 4,389 shares held by the John L. Gainer Declaration of Trust dated February 19, 2008 and (b) 16,231 shares of common stock issuable upon the exercise of options exercisable within 60 days of March 13, 2019. Dr. Gainer is a trustee of the revocable trust, and, as such, may be deemed to share beneficial ownership of such shares. Dr. Gainer expressly disclaims beneficial ownership of any such shares except to the extent of his pecuniary interest therein.

⁽⁵⁾ Consists of (a) 294 shares held for the benefit of Mr. Giles in his individual retirement account, (b) 53,513 shares held by MTG Investment Holdings, LLC and (c) 12,373 shares of common stock issuable upon the exercise of options exercisable within 60 days of March 13, 2019. Mr. Giles is the sole member of MTG Investment Holdings, LLC and may be deemed to be the beneficial owner of such securities. Mr. Giles disclaims beneficial ownership of such securities except to the extent of his pecuniary interest therein.

(6) Consists of (a) 1,654 shares held by Mr. Levin directly and (b) 12,103 shares of common stock issuable upon the exercise of options exercisable within 60 days of March 13, 2019.

(7) Consists of (a) 1,706 shares held directly by Mr. Adams directly, (b) 631 shares held jointly with Mr. Adams' wife, (c) 1,260 shares held for the benefit of Mr. Adams in his 401(k) retirement account and (d) 13,321 shares of common stock issuable upon the exercise of options exercisable within 60 days of March 13, 2019.

(8) Consists of shares of common stock issuable upon the exercise of options exercisable within 60 days of March 13, 2019.

(9) Consists of (a) 9,280 shares held by Mr. Byrne directly and (b) 11,647 shares of common stock issuable upon the exercise of options exercisable within 60 days of March 13, 2019.

(10) Consists of shares of common stock issuable upon the exercise of options exercisable within 60 days of March 13, 2019.

(11) Excludes shares of our common stock beneficially owned by Mr. Shealy, who is not an executive officer of the Company as of March 13, 2019. Includes 94,147 shares of common stock issuable upon the exercise of options exercisable within 60 days of March 13, 2019.

*Indicates less than 1%.

ITEM 13. CERTAIN RELATIONSHIPS AND RELATED TRANSACTIONS, AND DIRECTOR INDEPENDENCE

Overview

Our Audit Committee is charged with the responsibility of reviewing and approving or ratifying all related person transactions in accordance with the Listing Rules of The NASDAQ Stock Market and other applicable law, rules and regulations and any related policies and procedures adopted by or on behalf of the Company and then in effect.

Since January 1, 2018 there have been no transactions to which we have been a party in which (i) the amount involved in the transaction exceeds \$120,000 and (ii) any of our directors, executive officers or, to our knowledge, beneficial owners of more than 5% of our capital stock had or will have a direct or indirect material interest.

For more information regarding the independence of our directors, see "Item 10. Directors, Executive Officers and Corporate Governance."

ITEM 14. PRINCIPAL ACCOUNTING FEES AND SERVICES

Independent Auditor's Fees

The table below presents fees billed to us for professional services rendered by KPMG, our current independent registered public accounting firm, for the years ended December 31, 2018 and December 31, 2017.

	Aggregate Amount Billed	
	2018	2017
Audit Fees	\$ 516,149	\$ 366,623
Audit-Related Fees	\$ —	\$ —
Tax Fees ⁽¹⁾	\$ —	\$ 27,003
All other Fees	\$ —	\$ —

(1) Tax Fees consist of fees payable to KPMG for an analysis of the Company's net operating losses.

Pre-Approval Policies and Procedures

The Audit Committee has adopted procedures pursuant to which all audit, audit-related and tax services and all permissible non-audit services provided by our independent registered public accounting firm must be pre-approved by the Audit Committee. All services rendered by KPMG during 2018 and 2017 were permissible under applicable laws and regulations and were approved in advance by the former Audit Committee in accordance with the rules adopted by the SEC in order to implement requirements of the Sarbanes-Oxley Act of 2002 other than *de minimis* non-audit services allowed under applicable law.

PART IV

ITEM 15. EXHIBITS, FINANCIAL STATEMENT SCHEDULES

Our financial statements are included in Item 8 of Part II of this report.

The exhibits to this report are listed on the Exhibit Index to this report. A copy of any of the exhibits listed will be furnished at a reasonable cost, upon receipt from any person of a written request for any such exhibit. Such request should be sent to Diffusion Pharmaceuticals Inc., 1317 Carlton Avenue, Suite 200, Charlottesville, Virginia 22902, Attention: Stockholder Information. The Exhibit Index indicates each management contract or compensatory plan or arrangement required to be filed as an exhibit to this report.

**DIFFUSION PHARMACEUTICALS INC.
EXHIBIT INDEX TO ANNUAL REPORT ON FORM 10-K
FOR THE YEAR ENDED DECEMBER 31, 2018**

Exhibit No.	Description	Method of Filing
3.1	<u>Certificate of Incorporation of Diffusion Pharmaceuticals Inc., as amended</u>	Filed herewith
3.2	<u>Bylaws of Diffusion Pharmaceuticals Inc., as amended</u>	Incorporated by reference to Exhibit 3.4 to the registrant's annual report on Form 10-K for the year ended December 31, 2015
3.3	<u>Certificate of Designation of Preferences, Rights and Limitations of the Series A Convertible Preferred Stock of Diffusion Pharmaceuticals Inc.</u>	Incorporated by reference to Exhibit 3.1 to the registrant's current report on Form 8-K filed on March 15, 2017
3.4	<u>Certificate of Retirement, as filed with the Secretary of State of the State of Delaware</u>	Incorporated by reference to Exhibit 3.1 to the registrant's current report on Form 8-K filed on August 14, 2018
4.1	<u>Form of Warrant issued to Investors in the 2017 Private Placement by Diffusion Pharmaceuticals Inc.</u>	Incorporated by reference to Exhibit 4.1 to the registrant's current report on Form 8-K filed on March 15, 2017
4.2	<u>Form of 2018 Common Stock Warrant</u>	Incorporated by reference to Exhibit 4.1 to the registrant's current report on Form 8-K filed on January 19, 2018
4.3	<u>Form of 2018 Underwriters' Warrant</u>	Incorporated by reference to Exhibit 4.2 to the registrant's current report on Form 8-K filed on January 22, 2018
10.1	<u>Employment Agreement, dated as of September 6, 2016, by and between David G. Kalergis and Diffusion Pharmaceuticals Inc.*</u>	Incorporated by reference to Exhibit 10.1 to the registrant's current report on Form 8-K as filed on September 8, 2016
10.2	<u>Employment Agreement, dated as of October 12, 2016, by and between Ben L. Shealy and Diffusion Pharmaceuticals Inc.*</u>	Incorporated by reference to Exhibit 10.1 to the registrant's current report on Form 8-K as filed on October 13, 2016
10.3	<u>Separation Letter, effective as of September 26, 2018, by and between Ben L. Shealy and Diffusion Pharmaceuticals Inc.*</u>	Incorporated by reference to Exhibit 10.1 to the registrant's current report on Form 8-K as filed on September 27, 2018
10.4	<u>Amended and Restated Employment Agreement, dated as of September 21, 2018, by and between William Karl Hornung and Diffusion Pharmaceuticals Inc.*</u>	Incorporated by reference to Exhibit 10.2 to the Company's Current Report on Form 8-K filed September 27, 2018

10.5	<u>Diffusion Pharmaceuticals Inc. 2015 Equity Incentive Plan**</u>	Incorporated by reference to Exhibit 10.2 to the registrant's current report on Form 8-K as filed on June 18, 2015
10.6	<u>Amendment No. 1 to Diffusion Pharmaceuticals Inc. 2015 Equity Incentive Plan</u>	Incorporated by reference to Appendix B to the registrants definitive proxy statement on Schedule 14A filed on June 10, 2016
10.7	<u>Form of Diffusion Pharmaceuticals Inc. Stock Option Award Agreement*</u>	Incorporated by reference to Exhibit 10.5 to the registrant's annual report on Form 10-K for the year ended December 31, 2017
10.8	<u>Form of Diffusion Pharmaceuticals LLC Stock Option Award Agreement*</u>	Incorporated by reference to Exhibit 10.24 to the registrant's annual report on Form 10-K for the year ended December 31, 2015
10.9	<u>Form of 2015 Incentive Stock Option Agreement under the Diffusion Pharmaceuticals Inc. 2015 Equity Incentive Plan*</u>	Incorporated by reference to Exhibit 10.3 to the registrant's current report on Form 8-K filed on June 18, 2015
10.10	<u>Form of 2015 Non-Statutory Stock Option Agreement under the Diffusion Pharmaceuticals Inc. 2015 Equity Incentive Plan*</u>	Incorporated by reference to Exhibit 10.4 to the registrant's current report on Form 8-K filed on June 18, 2015
10.11	<u>Form of Stock Option Agreement between the Company and certain former Executive Officers*</u>	Incorporated by reference to Exhibit 10.12 to the registrant's annual report on Form 10-K for the fiscal year ended December 31, 2014
10.12	<u>Form of Stock Option Agreement between the Company and certain former Directors*</u>	Incorporated by reference to Exhibit 10.13 to the registrant's annual report on Form 10-K for the fiscal year ended December 31, 2014
10.13	<u>Form of Indemnification Agreement between Diffusion Pharmaceuticals Inc. and each of its Directors and Officers*</u>	Incorporated by reference to Exhibit 10.3 to the registrant's annual report on Form 10-K for the year ended December 31, 2015
10.14	<u>Lease Agreement, dated March 31, 2017, by and between Diffusion Pharmaceuticals Inc. and One Carlton LLC</u>	Incorporated by reference to Exhibit 10.4 to the registrant's quarterly report on Form 10-Q for the quarter ended March 31, 2017
10.15	<u>Contingent Value Rights Agreement, dated as of January 8, 2016, by and between Diffusion Pharmaceuticals Inc. and Computershare, Inc., as Rights Agent</u>	Incorporated by reference to Exhibit 10.2 to the registrant's current report on Form 8-K filed on January 8, 2016
21.1	<u>Subsidiaries of Diffusion Pharmaceuticals Inc.</u>	Filed herewith
23.1	<u>Consent of KPMG LLP, independent registered public accounting firm</u>	Filed herewith
31.1	<u>Certification of Chief Executive Officer Pursuant to Section 302 of the Sarbanes-Oxley Act of 2002 and SEC Rule 13a-14(a)</u>	Filed herewith
31.2	<u>Certification of Principal Financial Officer Pursuant to Section 302 of the Sarbanes-Oxley Act of 2002 and SEC Rule 13a-14(a)</u>	Filed herewith
32.1	<u>Certification Pursuant to 18 U.S.C. Section 1350, as Adopted Pursuant to Section 906 of the Sarbanes-Oxley Act of 2002</u>	Furnished herewith
101	The following materials from the registrant's annual report on Form 10-K for the year ended December 31, 2018, formatted in XBRL (Extensible Business Reporting Language): (i) Consolidated Balance Sheets, (ii) Consolidated Statements of Operations, (iii) Consolidated Statements of Cash Flows, and (iv) Notes to Consolidated Financial Statements	Filed herewith

* A management contract or compensatory plan or arrangement.

ITEM 16. FORM 10-K SUMMARY

None.

SIGNATURES

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

Dated: March 19, 2019

DIFFUSION PHARMACEUTICALS INC.

By: /s/ David G. Kalergis
David G. Kalergis
Chairman and Chief Executive Officer
(Principal Executive Officer)

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

<u>Name and Signature</u>	<u>Title</u>	<u>Date</u>
<u>/s/ David G. Kalergis</u> David G. Kalergis	Chairman of the Board and Chief Executive Officer (Principal Executive Officer)	March 19, 2019
<u>/s/ William Hornung</u> William Hornung	Chief Financial Officer (Principal Financial and Accounting Officer)	March 19, 2019
<u>/s/ John L. Gainer, Ph.D.</u> John L. Gainer, Ph.D.	Director	March 19, 2019
<u>/s/ Robert Adams</u> Robert Adams	Director	March 19, 2019
<u>/s/ Mark T. Giles</u> Mark T. Giles	Director	March 19, 2019
<u>/s/ Alan Levin</u> Alan Levin	Director	March 19, 2019

**CERTIFICATE OF INCORPORATION
OF
DIFFUSION PHARMACEUTICALS INC.
(AS AMENDED)**

**ARTICLE I
NAME**

The name of the corporation is Diffusion Pharmaceuticals Inc. (the “Corporation”).

**ARTICLE II
REGISTERED OFFICE AND AGENT**

The address of the registered office of the Corporation in the State of Delaware is 615 South Dupont Hwy., in the City of Dover, Zip Code of 19901, County of Kent. The name of the registered agent of the Corporation at that address is National Corporate Research, Ltd.

**ARTICLE III
PURPOSE**

The purpose of the Corporation is to engage in any lawful act or activity for which a corporation may be organized under the General Corporation Law of the State of Delaware (“DGCL”).

**ARTICLE IV
CAPITAL STOCK**

A. The total number of shares of common stock which the Corporation shall have authority to issue is 1,000,000,000, at a par value of \$0.001 per share (“Common Stock”), and the total number of shares of preferred stock which the Corporation shall have authority to issue is 30,000,000, at a par value of \$0.001 per share (“Preferred Stock”).

1. Common Stock. All preferences, voting powers, relative, participating, optional or other special rights and privileges, and qualifications, limitations, or restrictions of the Common Stock are expressly made subject and subordinate to those that may be fixed with respect to any shares of the Preferred Stock. Except as otherwise required by law or this Certificate of Incorporation, each share of Common Stock shall entitle the holder thereof to one (1) vote, in person or by proxy, on each matter submitted to a vote of stockholders of the Corporation. Subject to the preferential rights of the Preferred Stock, the holders of shares of Common Stock shall be entitled to receive, when and if declared by the Board of Directors, out of the assets of the Corporation which are by law available therefor, dividends payable either in cash, in property or in shares of capital stock. In the event of any dissolution, liquidation or winding up of the affairs of the Corporation, after distribution in full of the preferential amounts, if any, to be distributed to the holders of shares of the Preferred Stock, holders of Common Stock shall be entitled, unless otherwise provided by law or this Certificate of Incorporation, to receive all of the remaining assets of the Corporation of whatever kind available for distribution to stockholders ratably in proportion to the number of shares of Common Stock held by them respectively.

2. Preferred Stock. The Preferred Stock may be issued from time to time in one or more series, as determined by the Board of Directors of the Corporation (the "Board of Directors"). The Board of Directors is expressly authorized to provide for the issue, in one or more series, of all or any of the remaining shares of Preferred Stock and, in the resolution or resolutions providing for such issue, to establish for each such series the number of its shares, the voting powers, full or limited, of the shares of such series, or that such shares shall have no voting powers, and the designations, preferences and relative, participating, optional or other special rights, if any, of the shares of such series, and any qualifications, limitations or restrictions thereof. The powers, preferences and relative, participating, optional and other special rights of each series of preferred stock and the qualifications, limitations or restrictions thereof, if any, may differ from those of any and all other series at any time outstanding. The Board of Directors is further expressly authorized to increase or decrease (but not below the number of shares of any such series then outstanding) the number of shares of any series, the number of which was fixed by it, subsequent to the issuance of shares of such series then outstanding, subject to the powers, preferences and rights, and the qualifications, limitations and restrictions thereof stated in this Certificate of Incorporation or the resolution of the Board of Directors originally fixing the number of shares of such series. If the number of shares of any series is so decreased, then the shares constituting such decrease shall resume the status which they had prior to the adoption of the resolution originally fixing the number of shares of such series.

Effective upon the effective time of the Certificate of Amendment of the Certificate of Incorporation filed on August 17, 2016 with the Secretary of State of the State of Delaware (the "Effective Time"), each ten (10) shares of Common Stock issued and outstanding immediately prior to the Effective Time shall, automatically and without the necessity for any further action, be changed, reclassified and combined into one (1) share of Common Stock (the "Reverse Stock Split"). No fractional shares shall be issued in connection with the Reverse Stock Split. Stockholders who otherwise would be entitled to receive fractional shares of Common Stock shall have that rounded up to one additional whole share. Each certificate that immediately prior to the Effective Time represented shares of Common Stock ("Old Certificates") shall thereafter represent that number of shares of Common Stock into which the shares of Common Stock represented by the Old Certificate shall have been combined, subject to the elimination of fractional shares as described above.

Effective upon the effective time of the Certificate of Amendment of the Certificate of Incorporation filed on December 13, 2018 with the Secretary of State of the State of Delaware (the "2018 Effective Time"), each fifteen (15) shares of Common Stock issued and outstanding immediately prior to the 2018 Effective Time shall, automatically and without the necessity of any further action, be changed, reclassified and combined into one (1) share of Common Stock (the "2018 Reverse Stock Split"). No fractional shares shall be issued in connection with the 2018 Reverse Stock Split. Stockholders who otherwise would be entitled to receive fractional shares of Common Stock shall have that rounded up to one additional whole share. Each certificate that immediately prior to the 2018 Effective Time represented shares of Common Stock ("2018 Old Certificates"), shall thereafter represent that number of shares of Common Stock into which the shares of Common Stock represented by the 2018 Old Certificate shall have been combined, subject to the elimination of fractional shares as described above.

ARTICLE V
EXCULPATION AND INDEMNIFICATION

A. Limitation of Liability. A director of the Corporation shall not be personally liable to the Corporation or its stockholders for monetary damages for breach of fiduciary duty as a director, except to the extent such exemption from liability or limitation thereof is not permitted under the DGCL as it presently exists or may hereafter be amended. Any amendment, modification or repeal of the foregoing sentence shall not adversely affect any right arising prior to the time of such amendment, modification or repeal.

B. Right of Indemnification. The Corporation shall indemnify and hold harmless, to the fullest extent permitted by applicable law as it presently exists or may hereafter be amended, any person (a “Covered Person”) who was or is made or is threatened to be made a party or is otherwise involved in any action, suit or proceeding, whether civil, criminal, administrative or investigative (a “Proceeding”), by reason of the fact that he or she, or a person for whom he or she is the legal representative, is or was a director, officer, employee or agent of the Corporation or, while a director, officer, employee or agent of the Corporation, is or was serving at the request of the Corporation as a director, officer, employee or agent of another corporation or of a partnership, joint venture, trust, enterprise or nonprofit entity, including service with respect to employee benefit plans, against all liability and loss suffered and expenses (including attorneys’ fees) reasonably incurred by such Covered Person. Notwithstanding the preceding sentence, except as otherwise provided in section D of this Article V, the Corporation shall not be required to indemnify a Covered Person in connection with a Proceeding (or part thereof) commenced by such Covered Person unless the commencement of such Proceeding (or part thereof) by the Covered Person was authorized in the specific case by the Board of Directors.

C. Prepayment of Expenses. The Corporation shall to the fullest extent not prohibited by applicable law pay the expenses (including attorneys’ fees) incurred by a Covered Person in defending any Proceeding in advance of its final disposition, provided, however, that, to the extent required by law, such payment of expenses in advance of the final disposition of the Proceeding shall be made only upon receipt of an undertaking by the Covered Person to repay all amounts advanced if it should be ultimately determined that the Covered Person is not entitled to be indemnified under this Article V or otherwise.

D. Claims. If a claim for indemnification (following the final disposition of the Proceeding with respect to which indemnification is sought, including any settlement of such Proceeding) or advancement of expenses under this Article V is not paid in full within thirty (30) days after a written claim therefor by the Covered Person has been received by the Corporation, the Covered Person may file suit to recover the unpaid amount of such claim and, if successful in whole or in part, shall be entitled to be paid the expense of prosecuting such claim to the fullest extent permitted by applicable law. In any such action the Corporation shall have the burden of proving that the Covered Person is not entitled to the requested indemnification or advancement of expenses under this Article V and applicable law.

E. Non-Exclusivity of Rights. The rights conferred on any Covered Person by this Article V shall not be exclusive of any other rights which such Covered Person may have or hereafter acquire under any statute, any other provision of this Certificate of Incorporation, the Bylaws of the Corporation, or any agreement, vote of stockholders or disinterested directors or otherwise.

F. Insurance. The Corporation may purchase and maintain insurance on behalf of any person who is or was a director, officer, employee or agent of the Corporation, or is or was serving at the request of the Corporation as a director, officer, employee or agent of another corporation or of a partnership, joint venture, trust, enterprise or nonprofit entity, including service with respect to employee benefit plans, against any liability asserted against such person and incurred by such person in any such capacity, or arising out of such person's status as such, whether or not the Corporation would have the power to indemnify such person against such liability under this Article V, the DGCL or otherwise.

G. Amendment or Repeal. Any right to indemnification or to advancement of expenses of any Covered Person arising hereunder shall not be eliminated or impaired by an amendment to or repeal of this Article V after the occurrence of the act or omission that is the subject of the civil, criminal, administrative or investigative action, suit or proceeding for which indemnification or advancement of expenses is sought.

H. Other Indemnification and Advancement of Expenses. This Article V shall not limit the right of the Corporation, to the extent and in the manner permitted by law, to indemnify and to advance expenses to persons other than Covered Persons when and as authorized by appropriate corporate action.

ARTICLE VI MANAGEMENT

For the management of the business and for the conduct of the affairs of the Corporation, and in further definition, limitation and regulation of the powers of the Corporation, of its directors and of its stockholders or any class thereof, as the case may be, it is further provided that:

A. The management of the business and the conduct of the affairs of the Corporation shall be vested in the Board of Directors. The Board of Directors shall fix the number of directors that constitute the whole Board of Directors in the manner provided in the Bylaws of the Corporation, subject to any restrictions that may be set forth in this Certificate of Incorporation.

B. In furtherance and not in limitation of the powers conferred by statute, the Board of Directors is expressly empowered to adopt, amend or repeal the Bylaws of the Corporation or adopt new Bylaws of the Corporation without any action on the part of the stockholders. Any adoption, amendment or repeal of the Bylaws of the Corporation by the Board of Directors shall require the approval of a majority of the directors then in office. The stockholders of the Corporation shall also have the power to adopt, amend or repeal the Bylaws of the Corporation; provided, however, that, in addition to any vote of the holders of any class or series of stock of the Corporation required by law or by this Certificate of Incorporation, the affirmative vote of the holders of at least sixty-six and two-thirds percent (66-2/3%) of the voting power of all of the then-outstanding shares of the capital stock of the Corporation entitled to vote generally in the election of directors, voting together as a single class, shall be required to adopt, amend or repeal any provision of the Bylaws of the Corporation.

C. The Corporation reserves the right to amend, alter, change or repeal any provision contained in this Certificate of Incorporation, in the manner now or hereafter prescribed by the DGCL, and all rights conferred upon stockholders herein are granted subject to this reservation.

**ARTICLE VII
STOCKHOLDER MEETINGS**

Meetings of stockholders may be held within or without the State of Delaware, as the Bylaws of the Corporation may provide. Elections of directors need not be by written ballot unless and except to the extent that the Bylaws of the Corporation so provide. Any action required to or which may be taken at a meeting of stockholders of the corporation may be taken without a meeting if authorized by a writing signed by all of the holders of shares who would be entitled to vote upon the action at a meeting for such purpose.

**ARTICLE VIII
INCORPORATOR**

The name and mailing address of the incorporator of the Corporation are as follows:

Amy E. Culbert
Oppenheimer Wolff & Donnelly LLP
Campbell Mithun Tower, Suite 2000
222 South Ninth Street
Minneapolis, MN 55402

**ARTICLE IX
EFFECTIVE TIME**

This Certificate of Incorporation shall be effective as of 5:00 p.m. Eastern Time on June 18, 2015.

The undersigned, being the incorporator named above, for the purpose of forming a corporation pursuant to the DGCL, does hereby make this Certificate of Incorporation, hereby acknowledging, declaring and certifying that the foregoing Certificate of Incorporation is the undersigned's act and deed and the facts herein stated are true, and accordingly has hereunto set the undersigned's hand this 17th day of June, 2015.

INCORPORATOR:

By: /s/ Amy E. Culbert
Amy E. Culbert

Amended: January 8, 2016; August 17, 2016; January 23, 2017; March 13, 2017; August 13, 2018; December 13, 2018.

SUBSIDIARIES OF THE REGISTRANT

Name of Subsidiary	State or Other Jurisdiction of Incorporation or Organization	Direct or Indirect Ownership Interest by Company
Canterbury Laboratories, LLC	DE	100%
Hygeia Therapeutics, Inc.	DE	100%
VasculoMedics, Inc.	DE	100%
Diffusion Pharmaceuticals LLC	VA	100%

Consent of Independent Registered Public Accounting Firm

The Board of Directors
Diffusion Pharmaceuticals Inc.:

We consent to the incorporation by reference in the registration statements (No. 333-206408, No. 333-206409, No. 333-218060 and No. 333-226782) on Form S-8, (No. 333-222203) on Form S-1, and (No. 333-218062 and No. 333-222879) on Form S-3 of Diffusion Pharmaceuticals Inc. of our report dated March 19, 2019, with respect to the consolidated balance sheets of Diffusion Pharmaceuticals Inc. as of December 31, 2018 and 2017, and the related consolidated statements of operations, changes in stockholders' equity, and cash flows for each of the years in the two-year period ended December 31, 2018, and the related notes, which report appears in the December 31, 2018 annual report on Form 10-K of Diffusion Pharmaceuticals Inc.

Our report dated March 19, 2019, contains an explanatory paragraph that states that the Company has suffered recurring losses from operations, has limited resources available to fund current research and development activities, and will require substantial additional financing to continue to fund its research and development activities that raise substantial doubt about its ability to continue as a going concern. The consolidated financial statements do not include any adjustments that might result from the outcome of this uncertainty.

[(signed) KPMG LLP]

McLean, Virginia
March 19, 2019

DIFFUSION PHARMACEUTICALS INC.
CERTIFICATION OF CEO PURSUANT TO SECTION 302 OF
THE SARBANES-OXLEY ACT OF 2002
CERTIFICATION

I, David G. Kalergis, certify that:

1. I have reviewed this annual report on Form 10-K of Diffusion Pharmaceuticals 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.

Date: March 19, 2019

/s/ David G. Kalergis

David G. Kalergis
Chairman and Chief Executive Officer
(Principal Executive Officer)

DIFFUSION PHARMACEUTICALS INC.
CERTIFICATION OF PFO PURSUANT TO SECTION 302 OF
THE SARBANES-OXLEY ACT OF 2002
CERTIFICATION

I, William K. Hornung, certify that:

1. I have reviewed this annual report on Form 10-K of Diffusion Pharmaceuticals 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.

Date: March 19, 2019

/s/ William K. Hornung

William K. Hornung
Chief Financial Officer (Principal Financial and
Accounting Officer)

**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 Diffusion Pharmaceuticals Inc. (the "Company") for the period ended December 31, 2018 as filed with the Securities and Exchange Commission on the date hereof (the "Report"), we, David G. Kalergis and William K. Hornung, Chairman and Chief Executive Officer and Chief Financial Officer, respectively, 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 our knowledge:

- (1) The Report fully complies with the requirements of Section 13(a) or 15(d) of the Securities Exchange Act of 1934; and
- (2) The information contained in the Report fairly presents, in all material respects, the financial condition and results of operations of the Company.

March 19, 2019

/s/ David G. Kalergis
David G. Kalergis
Chairman and Chief Executive Officer

/s/ William K. Hornung
William K. Hornung
Chief Financial Officer