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, 2021
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	**30-0645032**
(State or Other Jurisdiction of Incorporation or Organization)	(I.R.S. Employer Identification No)
300 East Main Street, Suite 201	
Charlottesville, VA	**22902**
(Address of Principal Executive Offices)	(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	**Trading Symbol**	**Name of Each Exchange on Which Registered**
Common Stock, par value $0.001 per share	DFFN	The 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 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.

Large accelerated filer ☐
Non-accelerated filer ☒
Emerging growth company ☐

Accelerated filer ☐
Smaller reporting 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. ☐

Indicated by check mark whether the registrant has filed a report on and attestation to its management's assessment of the effectiveness of its internal control over financial reporting under Section 404(b) of the Sarbanes-Oxley Act (15 U.S.C. 7262(b)) by the registered public accounting firm that prepared or issued its audit report. ☐

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 beneficially owned by non-affiliates of the registrant, calculated based upon the closing sale price of the common stock as quoted by the Nasdaq Capital Market on June 30, 2021 (the last business day of the registrant's second fiscal quarter), was approximately $74.3 million.

As of March 14, 2022, 101,924,581 shares of common stock of the registrant were outstanding.

DOCUMENTS INCORPORATED BY REFERENCE

TABLE OF CONTENTS

INTRODUCTORY NOTES

Note Regarding Company References and Other Defined Terms

Unless the context otherwise requires, in this Annual Report, (i) references to the "Company," "we," "our," or "us" refer to Diffusion Pharmaceuticals Inc. and its subsidiaries and (ii) references to "common stock" refer to the common stock, par value $0.001 per share, of the Company. We have also used several other defined terms in this Annual Report, which are explained or defined below:

Term	Definition
2015 Equity Plan	Diffusion Pharmaceuticals Inc. 2015 Equity Incentive Plan, as amended
2017 Tax Act	Tax Cuts and Jobs Act of 2017
401(k) Plan	Diffusion Pharmaceuticals Inc. 401(k) Defined Contribution Plan
Affordable Care Act	U.S. Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act
Altitude Trial	our ongoing Phase 1b clinical trial evaluating TSC in normal healthy volunteers subjected to incremental levels of physical exertion while exposed to hypoxic and hypobaric conditions, or "simulated altitude"
ANDA	abbreviated new drug application
Annual Report	this Annual Report on Form 10-K
API	active pharmaceutical ingredient
ASC	Accounting Standard Codification of the FASB
ASC 815-40	ASC 815-40, *Derivatives and Hedging, Contracts in an Entity's Own Equity*
ASUs	Accounting Standards Updates of the FASB
Bid Price Rule	the minimum bid price requirement contained in Nasdaq Listing Rule 5550(a)(2)
Black-Scholes Model	Black-Scholes-Merton derivative investment instrument pricing model
Board	our board of directors
Bylaws	the Company's bylaws, as amended
Carlton Lease	the Lease Agreement, dated March 31, 2017, related to our prior corporate headquarters located at 1317 Carlton Avenue in Charlottesville, Virginia
COVID-19	Corona Virus Disease 2019, the novel coronavirus disease known as COVID-19, caused by severe acute respiratory syndrome coronavirus 2 viral infection
COVID Trial	our Phase 1b clinical trial evaluating TSC in hospitalized COVID-19 patients, completed in February 2021
cGMP	current good manufacturing practices
CMO	contract manufacturing organization
CMS	Centers for Medicare & Medicaid Services
CRO	contract research organization
CTA	clinical trial application
December 2019 Offering	our registered direct public offering and sale of 6,266,787 shares of common stock and concurrent private placement of warrants to purchase up to 6,266,787 shares of common stock completed in December 2019
Diffusion LLC	Diffusion Pharmaceuticals LLC, a Virginia limited liability company and our wholly owned subsidiary
DLCO	diffusion capacity of lung for carbon monoxide
Dodd-Frank Act	Dodd-Frank Wall Street Reform and Consumer Protection Act of 2010
E.U.	European Union
Exchange Act	Securities Exchange Act of 1934, as amended
FASB	Financial Accounting Standards Board
FDA	U.S. Food and Drug Administration
FDC Act	Federal Food, Drug, and Cosmetic Act

February 2021 Offering	our public offering and sale of 33,658,538 shares of common stock completed in February 2021
G&A	general and administrative
GAAP	U.S. generally accepted accounting principles
GBM	glioblastoma multiforme brain cancer
GBM Trial	our Phase 3 clinical trial evaluating TSC in a newly diagnosed inoperable GBM patient population, initiated in December 2017
GCP	good clinical practice
GLP	good laboratory practice
HIPAA	Health Insurance Portability and Accountability Act of 1996
HITECH	Health Information Technology for Economic and Clinical Health Act of 2009
Hypoxic Solid Tumor Program	our ongoing clinical development program to evaluate TSC as an adjunct to standard of care therapy for hypoxic solid tumors, first announced in November 2021
ILD	interstitial lung disease
ILD-DLCO Trial	our ongoing Phase 2a clinical trial evaluating TSC in patients with previously diagnosed ILD who have a baseline DLCO test result that is abnormal using DLCO as a surrogate measure of oxygen transfer efficiency
IMM	irreversible morbidity and mortality
IND	investigational new drug application
IPR&D	in-process research and development
IRB	institutional review board
May 2019 Offering	our registered direct public offering and sale of 1,317,060 shares of common stock and concurrent private placement of warrants to purchase up to 1,317,060 shares of common stock completed in May 2019
May 2020 Investor Warrant Exercise	the exercise of the Prior Warrant in May 2020 pursuant to a warrant exercise agreement
May 2020 Offering	our registered direct public offering and sale of 11,428,572 shares of common stock completed in May 2020
Nasdaq or NASDAQ	Nasdaq Stock Market, LLC
Nasdaq Staff	the staff of the listing qualifications department of Nasdaq
NDA	new drug application
NOL	net operating loss
November 2019 Offering	our public offering and sale of 5,104,429 shares of common stock, pre-funded warrants to purchase up to 6,324,143 shares of common stock, and warrants to purchase up to 22,857,144 shares of common stock completed in November 2019
Oxygenation Trials	collectively, the TCOM Trial, the Altitude Trial, and the ILD-DLCO Trial
Planned Phase 2 Hypoxic Tumor Trial	the first clinical trial in our Hypoxic Solid Tumor Program, which we currently expect to be a Phase 2 clinical trial commencing in the second half of 2022, subject to FDA feedback and the availability of clinical drug supply
Prior Warrant	a previously outstanding warrant to purchase up to 5,000,000 shares of common stock at an exercise price of $0.35 per share
R&D	research and development
Regulation S-K	Regulation S-K promulgated under the Securities Act
REMS	risk evaluation and mitigation strategy
Reverse Stock Split	the proposed reclassification and combination of all shares of our common stock outstanding at a ratio of not less than one-for-two and not greater than one-for-50, the approval of which will be voted on by our stockholders at the Special Meeting
SEC	U.S. Securities and Exchange Commission
Securities Act	Securities Act of 1933, as amended
SOX	Sarbanes-Oxley Act of 2002, as amended
Special Meeting	the special meeting of our stockholders to be held on April 14, 2022
Sunshine Act	Physician Payments Sunshine Act

Tax Code	U.S. Internal Revenue Code of 1986, as amended
TCOM	transcutaneous oxygen measurement
TCOM Trial	our Phase 1b clinical trial evaluating the effects of TSC on peripheral tissue oxygenation in healthy normal volunteers using a TCOM device, completed in March 2021
TSC	trans sodium crocetinate, our lead product candidate
U.S.	United States
USPTO	U.S. Patent and Trademark Office

Note Regarding Forward-Looking Statements

This Annual Report (including, for purposes of this Note Regarding Forward-Looking Statements, any information or documents incorporated herein by reference) includes express and implied forward-looking statements. 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 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, liquidity and prospects may differ materially from the forward-looking statements contained in this Annual Report. In addition, even if our results of operations, financial condition, liquidity, and prospects are consistent with the forward-looking statements contained in this Annual Report, they may not be predictive of actual results or reflect unanticipated developments in future periods.

Forward-looking statements appear in a number of places throughout this Annual Report. 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 also include statements regarding our intentions, beliefs, projections, outlook, analyses, or expectations, including our intentions, beliefs, projections, outlook, analyses, or expectations concerning, among other things:

- our ability to satisfy the continued listing requirements of the NASDAQ Capital Market or any other exchange on which our securities may trade in the future;
- the success and timing of our clinical and preclinical studies, including our ability to enroll subjects in our ongoing and planned clinical studies at anticipated rates and our ability to manufacture an adequate amount of drug supply for our studies;
- obtaining and maintaining intellectual property protection for our product candidates and our proprietary technology;
- the performance of third parties, including contract research organizations, manufacturers, suppliers, and outside consultants, to whom we outsource certain operational, staff and other functions;
- our ability to obtain additional financing in the future and continue as a going concern;
- our ability to obtain and maintain regulatory approval of our product candidates and, if approved, our products, including the labeling under any approval we may obtain;
- our plans and ability to develop and commercialize our product candidates and the outcomes of our research and development activities;
- our estimates regarding expenses, future revenues, capital requirements, and needs for additional financing;
- 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, the rate and degree of market acceptance of any of our product candidates that may be approved in the future, and our ability to serve those markets;
- the success of products that are or may become available which also target the potential markets for our product candidates;
- our ability to operate our business without infringing the intellectual property rights of others and the potential for others to infringe upon our intellectual property rights;
- any significant breakdown, infiltration, or interruption of our information technology systems and infrastructure;
- recently enacted and future legislation related to the healthcare system, including trends towards managed care and healthcare cost containment, the impact of any significant spending reductions or cost controls affecting publicly funded or subsidized healthcare programs, or any replacement, repeal, modification, or invalidation of some or all of the provisions of the Affordable Care Act;
- other regulatory developments in the U.S., E.U., and other foreign jurisdictions;
- uncertainties related to general economic, political, business, industry, and market conditions, including the ongoing COVID-19 pandemic; and
- other risks and uncertainties, including those discussed under the heading "Risk Factors" in this Annual Report and elsewhere in our other public filings.

As a result of these and other factors, known and unknown, actual results could differ materially from our intentions, beliefs, projections, outlook, analyses, or expectations expressed in any forward-looking statements in this Annual Report. Accordingly, we cannot assure you that the forward-looking statements contained in this Annual Report will prove to be accurate or that any such inaccuracy will not be material. You should also understand that it is not possible to predict or identify all such factors, and you should not consider any such list to be a complete set of all potential risk or uncertainties. In light of the foregoing and the significant uncertainties in these forward-looking statements, you should not regard these statements as a representation or warranty by us or any other person that we will achieve our objectives and plans in any specified time frame, or at all. For all forward-looking statements, we claim the protection of the safe harbor for forward-looking statements contained in the Private Securities Litigation Reform Act of 1995.

Any forward-looking statement that we make in this Annual Report speaks only as of the date of such statement, and, except as required by applicable law or by the rules and regulations of the SEC, 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 current and any prior period results are not intended to express any ongoing or future trends or indications of future performance, unless explicitly expressed as such, and should only be viewed as historical data.

Note Regarding Trademarks, Trade Names, and Service Marks

This Annual Report contains certain trademarks, trade names, and service marks of ours, including “DIFFUSIO2N.” All other trade names, trademarks, and service marks appearing in this Annual Report are, to the knowledge of Diffusion, the property of their respective owners. To the extent any such terms appear without the trade name, trademark, or service mark notice, such presentation is for convenience only and should not be construed as being used in a descriptive or generic sense.

PART I

ITEM 1. BUSINESS

Diffusion Pharmaceuticals: Enhancing Oxygen, Fueling Life

We are a biopharmaceutical company developing novel therapies that enhance the body's ability to deliver oxygen to the areas where it is needed most. Our lead product candidate, TSC, is being developed to enhance the diffusion of oxygen to tissues with low oxygen levels, also known as hypoxia, a serious complication of many of medicine's most intractable and difficult-to-treat conditions.

Our Strategy

Our goal is to become a leading biopharmaceutical company focused on the development and commercialization of novel therapies that enhance the body's ability to deliver oxygen to areas where it is needed most and improve treatment outcomes for patients suffering from conditions complicated by hypoxia. To achieve this strategy, we are focused on the following key objectives:

- ***Demonstrate the effects of TSC on the oxygenation pathway***. The results of our Oxygenation Trials – a series of three short-term, pharmacodynamic studies to evaluate the effects of TSC on different components of the oxygenation pathway that we expect to complete by the middle of 2022 – will be used to further inform the identification of potential indications appropriate for TSC and will guide the design of clinical trials aimed at supporting the commercialization of TSC as a treatment for conditions complicated by hypoxia. For additional information, see "*Business — Our Lead Product Candidate: Trans Sodium Crocetinate -- The TSC Oxygenation Trials: Demonstrating Proof of Concept, Dose Response Relationships, and Potential Indications for Future Development.*"

- ***Develop TSC as an adjunct treatment for hypoxic solid tumors***. The prevalence of hypoxic regions across numerous primary solid tumor types is believed to directly contribute to treatment resistance, whether it be radiotherapy, chemotherapy, or immunotherapy, increasing the metastatic potential of these tumors and the probability of unsuccessful treatment. We believe TSC's novel mechanism of action supports the objective of developing TSC as a treatment for hypoxic solid tumors because TSC's ability to enhance the oxygenation of hypoxic tissues may increase the effectiveness of standard-of-care radiation therapy and chemotherapy. Accordingly, in November 2021, we announced our Hypoxic Solid Tumor Program and our intent to commence our Planned Phase 2 Hypoxic Solid Tumor Trial in the second half of 2022. The data obtained during 2021 and early 2022 from our Oxygenation Trials and COVID Trial regarding TSC's effects on oxygenation, dose response characteristics, pharmacokinetics, and pharmacodynamics are being used to guide the design of this trial. Through the combination of this new data, our past experiences, and further analyses and discussions of all available data with our Scientific Advisory Board and other external advisors, we believe we now have the necessary information to design the Hypoxic Solid Tumor Program to be more efficient and increase our likelihood of success compared to the Company's past efforts to develop TSC as a cancer treatment, which were terminated in 2019 due to financial constraints. For additional information, see "*Business — Our Lead Product Candidate: Trans Sodium Crocetinate – Our Hypoxic Solid Tumor Program*."

- ***Accelerate development of TSC as a treatment for non-cancer indications***. Beyond cancer, hypoxia is a complicating factor in many other intractable and difficult-to-treat conditions, including cardiovascular diseases, cerebrovascular diseases, respiratory diseases, skin and soft tissue diseases, and neurodegenerative diseases. We have previously undertaken clinical studies of TSC in a variety of non-cancer indications, including interstitial lung disease, COVID-19, stroke, and peripheral artery disease, and have evaluated TSC in preclinical models in an even wider range of indications. Data that we expect to obtain from our ongoing Altitude and ILD-DLCO Trials may identify additional, non-oncology development opportunities. Although our primary near-term focus will be our Hypoxic Solid Tumor Program, we will continue to explore pathways to progress TSC's development in non-oncology indications through our preclinical studies. For additional information, see "*Business — Our Lead Product Candidate: Trans Sodium Crocetinate – TSC's Potential to Treat Other Conditions Complicated by Hypoxia*."

- ***Maximize the commercial value of our pipeline***. We have invested, and plan to continue to invest, significant time, effort, and resources into the development and maintenance of our intellectual property portfolio as we seek to retain worldwide development and commercial rights to our product candidates. In parallel with advancing our development programs, we will evaluate the commercial landscape for TSC with the intent of improving patient access to maximize our chances of commercial success, should the product be approved.

- ***Opportunistically acquire or in-license additional product candidates that complement TSC and our overall strategy***. We believe we can leverage what we have learned from the development of TSC and the significant skills and experience of our team to opportunistically identify and acquire or in-license novel product candidates that complement TSC and further our efforts to improve patient outcomes by enhancing standard-of-care therapy for conditions complicated by hypoxia. We also believe diversifying our asset portfolio through an acquisition or in-licensing would reduce our Company's overall risk profile as an investment.

Our Lead Product Candidate: Trans Sodium Crocetinate

Our lead product candidate, TSC, is being developed to enhance the diffusion of oxygen to tissues with low oxygen levels, also known as hypoxia.

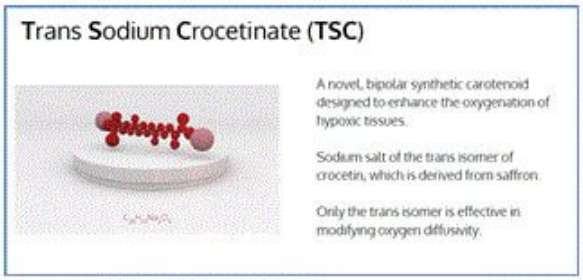
Hypoxia is a condition in which there is an insufficient supply of oxygen to meet the energy demands of the cells in a tissue (e.g., skeletal muscle). Hypoxia is associated with the pathophysiology of many of medicine's most intractable and difficult-to-treat conditions, including cancers, cardiovascular diseases, cerebrovascular diseases, respiratory diseases, skin and soft tissue diseases, and neurodegenerative diseases.

All currently approved treatments for hypoxia work by augmenting or supplementing the systemic availability of oxygen. For example, respirators use pressure to push oxygen across the lungs into the blood to increase oxygen concentration, certain medications and devices such as external mechanical pumps are designed to improve cardiac output, and blood transfusions are used to increase the concentration of red blood cells and oxygen-carrying hemoglobin molecules.

While these treatments are effective in certain circumstances, there are significant associated risks such as lung damage resulting from the use of respirators, toxic side effects and drug-to-drug interactions of medications that increase cardiac output, infections related to blood transfusions, and the risk of creating excessive oxygen-related tissue toxicity, or hyperoxia, by providing a patient with excessive amounts of oxygen, among others. In addition, in certain other indications, these currently approved therapies are ineffective in treating the associated hypoxia. For example, in the treatment of cancer, re-oxygenating hypoxic, cancerous tissue cells cannot typically be accomplished simply by increasing the systemic availability of oxygen.

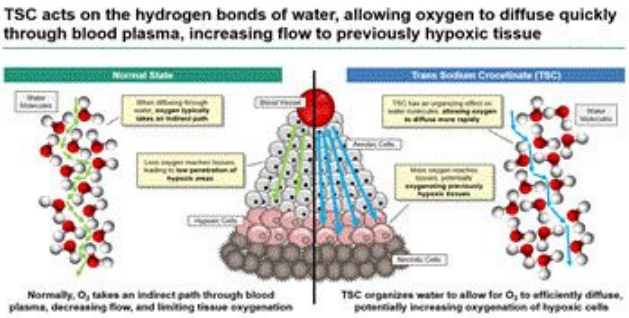
We believe TSC is the first therapy specifically designed to enhance the efficiency of the oxygen diffusion process. Furthermore, in animal models, TSC's diffusion-enhancing mechanism of action has been observed to affect hypoxic tissue preferentially while avoiding excessive oxygen-related tissue toxicity.

By supporting normal, physiologic levels of oxygen diffusion at the uptake and delivery points of the circulatory system, we believe TSC presents a significant opportunity to improve the current standard-of-care treatment for conditions complicated by hypoxia.



TSC's Mechanism of Action

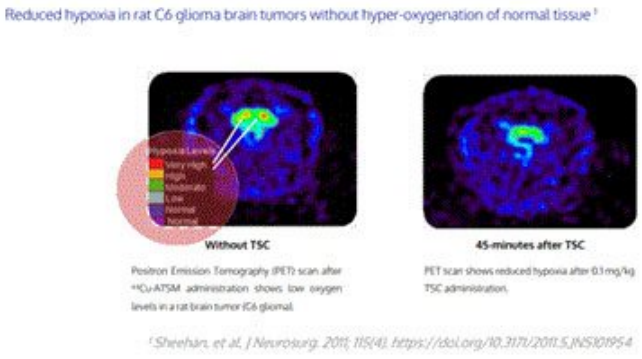
Blood plasma is approximately 90% water. The water molecules in the plasma are constantly moving, bound together in a loosely organized matrix by hydrogen bonds. TSC was designed to enhance the level of organization among the water molecules by increasing the amount of hydrogen bonding. This creates a less dense matrix of water molecules, reducing the resistance to oxygen diffusion across the concentration gradient.



Selected Preclinical Experiences

TSC has been evaluated in a variety of preclinical models intended to mimic relevant human conditions known to be complicated by hypoxia. In these studies, a variety of positive effects have been observed in connection with TSC administration, including:

- Reducing hypoxia in rat brain tumors without hyper-oxygenation of normal tissue;
- Improving survival in a rat brain tumor model when added to radiotherapy, whether alone or in combination with chemotherapy;
- Improving tissue oxygenation without hyper-oxygenation of normal tissue and reducing infarct size in a rat ischemic stroke model;
- Demonstrating a functional benefit in a rabbit ischemic stroke model, with or without tissue plasminogen activator at one-hour post-clot infection and with tissue plasminogen activator at three hours post-clot infection; and
- Improving levels of arterial partial pressure of blood oxygen in a rat model of acute respiratory distress syndrome.



Positron emission tomography scans showing reduction in hypoxia in a rat C6 glioma brain tumor model 45 min after TSC administration.

The TSC Oxygenation Trials: Demonstrating Proof of Concept, Dose Response Relationships, and Potential Indications for Future Development

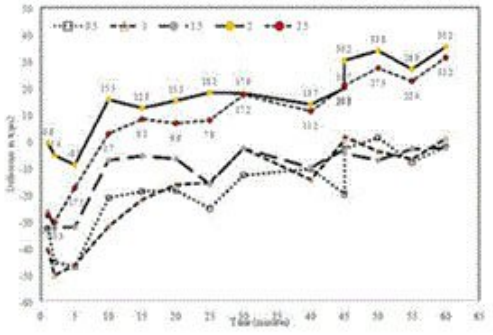
While our clinical trials evaluating TSC conducted prior to 2021 provided certain preliminary signals regarding TSC's mechanism of action and dose response characteristics, none of those studies were designed to demonstrate proof of concept by directly measuring TSC's effects on tissue oxygenation and a variety of questions remained regarding TSC's dose response characteristics, pharmacokinetics, and pharmacodynamics.

Given these identified gaps in our knowledge, in November 2020, we communicated our plan to design and execute our Oxygenation Trials, a series of short-term clinical studies using experimental models to evaluate the clinical effects of TSC on oxygenation, each designed to look at the effects of TSC on a different component of the oxygenation pathway. By quantifying the magnitude of effects of TSC on tissue oxygen levels and other direct clinical parameters assessing oxygen levels, and thereby demonstrating proof of concept of TSC's effects on tissue oxygenation, as well as supplementing our knowledge of TSC's dose response characteristics, pharmacokinetics and pharmacodynamics, we believe the data obtained from the Oxygenation Trials will allow us to significantly increase our clinical development strategy's likelihood of success.

TCOM Trial: TSC's Effects on Peripheral Tissue Oxygenation

In March 2021, we initiated and completed enrollment in the first of the Oxygenation Trials, our TCOM Trial. In June 2021, we reported a positive trend in peripheral tissue oxygenation as compared to placebo among participants receiving TSC that persisted through the duration of the one-hour, post-dosing measurement period. Although the magnitude of this effect was not statistically significant due to limitations in the study design, the trends in the primary endpoint data indicated an improvement in peripheral oxygenation with TSC with no evidence of hyperoxygenation.

The figure below was created during a supplemental analysis of the TCOM Trial results by subtracting the median response observed in the TCOM Trial's placebo group from the median response observed in each TSC dosage group at each of the measurement times during the one-hour period following dosing. These data highlight the persistent increase in peripheral tissue oxygenation relative to the placebo group through the duration of the one-hour measurement period following TSC administration, particularly at the two highest doses tested.



Effects of TSC on transcutaneous oxygen pressure.

We believe the TCOM Trial provides clinical evidence to support the hypothesis that TSC enhances the passive diffusion of oxygen from areas of high concentration to areas of low concentration without causing hyperoxygenation and that the data obtained from the study represent a positive and meaningful step towards the accomplishing of the Oxygenation Trials' strategic objectives originally set forth in November 2020. These data have and will continue to guide the next steps of our development strategy, including the design of our Hypoxic Solid Tumor Program.

Altitude Trial: TSC's Effects Under Induced Hypoxic Conditions

On November 22, 2021, we announced dosing of the first participants in our second Oxygenation Trial, the Altitude Trial. This study is a double-blind, randomized, placebo-controlled crossover study designed to evaluate the effects of TSC on maximal oxygen consumption and partial pressure of blood oxygen in normal healthy volunteers subjected to incremental levels of physical exertion while exposed to "simulated altitude." The study will enroll 30 healthy volunteers and give each volunteer a single dose of TSC at one of three different doses. Due to enrollment delays experienced during early 2022 related to the omicron variant wave of the COVID-19 pandemic, we now anticipate completing dosing in the Altitude Trial in the second quarter of 2022, with topline results reported within two months of study completion.

ILD-DLCO Trial: TSC's Effects on Oxygen Transfer Efficiency

On December 16, 2021, we announced dosing of the first patients in our third and final Oxygenation Trial, the ILD-DLCO Trial. This study is a double-blind, randomized, placebo-controlled, crossover study designed to evaluate the effects of TSC on the diffusion of carbon monoxide through the lungs, or DLCO, in patients with previously diagnosed ILD who have a baseline DLCO test result that is abnormal. DLCO is used in the study as a surrogate measure of oxygen transfer efficiency, or uptake, from the alveoli of the lungs through the plasma, and onto hemoglobin within red blood cells. The study will enroll 27 patients with confirmed ILD who will be randomized in a 2:1 ratio to a single dose of TSC or placebo via IV bolus. The study is statistically powered to evaluate the difference in effect of TSC versus placebo on improvement in DLCO measurements. In addition, patients will undergo a standard six-minute walk test intended to assess functional improvement in exercise capacity. Due to enrollment delays experienced during early 2022 related to the omicron variant wave of the COVID-19 pandemic, the effect of the omicron variant on patients with pulmonary diseases such as ILD, and staffing issues at the facilities where the ILD-DLCO Trial is being conducted, we now anticipate completing dosing in the ILD-DLCO Trial by the middle of 2022, with topline results reported within two months of study completion.

TSC's Demonstrated Clinical Safety Profile

TSC has been observed to be safe and well-tolerated at most doses tested in over 220 subjects included to-date in clinical studies at a variety of doses administered via intravenous infusion. Our clinical studies have included patients with a variety of medical conditions often complicated by hypoxia, including patients afflicted with GBM, peripheral artery disease with intermittent claudication, stroke, COVID-19, and interstitial lung disease. In each of these conditions and many others, hypoxia is a significant contributor to morbidity and mortality, and a considerable treatment obstacle for medical providers.

During 2021, we obtained additional data further demonstrating TSC's safety at higher doses and increased dosing frequencies from our COVID Trial and Oxygenation Trials. In the COVID Trial, completed in February 2021, TSC was administered on a different dosing regimen than any of our prior trials, with patients receiving an infusion multiple times per day for up to 15 days. In the TCOM Trial, based in part on a recommendation from the COVID Trial's safety monitoring committee, arms evaluating even higher doses of TSC were included. No dose-limiting toxicities or serious adverse events were observed among any patients or participants in the either trial, including those who received the highest tested doses of TSC.

Our Hypoxic Solid Tumor Program

We believe TSC's novel mechanism of action supports the objective of developing TSC as a treatment for hypoxic solid tumors because TSC's ability to enhance the oxygenation of hypoxic tissues may increase the effectiveness of standard-of-care radiation therapy and chemotherapy.

Solid tumors comprise approximately 90% of all adult cancers and, according to the American Cancer Society, it was expected that roughly 1.9 million new cancer cases would be diagnosed in the U.S. during 2021. It is also well-documented in the scientific literature that the prevalence of hypoxic regions across numerous primary solid tumor types directly contributes to treatment resistance, whether it be radiotherapy, chemotherapy, or immunotherapy, increasing the metastatic potential of these tumors and the probability of unsuccessful treatment.

Many of the challenges faced by practitioners in treating some of the most fatal and difficult-to-treat tumor types, including GBM, pancreatic cancer, and other solid tumors, are a product of those tumors' highly hypoxic nature. Cancerous tumors are specifically susceptible to developing hypoxia due to a combination of rapid growth, structural abnormalities of the tumor microvessels, and disturbed circulation within the tumor. Hypoxic conditions within the tumor microenvironment have numerous negative consequences for patient outcomes and treatment, including:

- increased resistance to ionizing radiation, chemotherapy, immunotherapy and other treatment methods;
- a more clinically aggressive phenotype;
- increased potential for invasive growth and tumor progression; and
- increased regional and distal tumor metastasis.

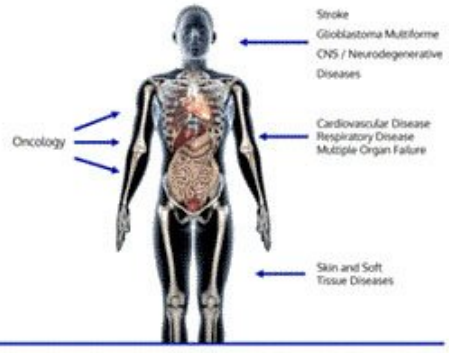
We have previously obtained and published evidence supporting TSC's ability to enhance oxygenation of C6 glioma tumors in animals, as well as clinical evidence of TSC's effects in unresectable GBM tumors from our previously completed Phase 2 clinical trial evaluating 59 patients with newly diagnosed GBM. This open-label, historically controlled trial demonstrated a favorable safety and tolerability profile for TSC when combined with standard of care treatment for GBM. Although not prospectively defined, a post hoc subgroup analysis of inoperable patients suggested a higher proportion of TSC-treated patients survived at two years compared to those in the historical control group.

In November 2021, based on the available preclinical and clinical data and the significant unmet medical need, we announced our intention to focus near-term efforts on developing TSC as an adjunct to standard of care therapy for hypoxic solid tumors. Through the combination of our past experiences, new knowledge gained from our Oxygenation Trials and COVID Trial regarding TSC's effects on oxygenation, dose response characteristics, pharmacokinetics, and pharmacodynamics, and further analyses and discussions of all available data with our Scientific Advisory Board and other external advisors, we believe we now have the necessary information to design the Hypoxic Solid Tumor Program to be more efficient and increase our likelihood of success compared to the Company's past efforts to develop TSC as a cancer treatment, which were terminated in 2019 due to financial constraints.

As part of the ongoing design of our Planned Phase 2 Hypoxic Tumor Trial – the first trial in our Hypoxic Solid Tumor Program which we currently expect to commence in the second half of 2022, subject to FDA feedback and the availability of clinical drug supply – we are currently drafting a trial protocol which we intend to file with the FDA. In parallel, we will continue our work to optimize the TSC manufacturing process and support the continued availability of high-quality drug product and undertake preclinical studies and other opportunities to continue developing data designed to demonstrate TSC's potential uses in a broad spectrum of non-cancer indications.

TSC's Potential to Treat Other Conditions Complicated by Hypoxia

Beyond cancer, hypoxia is a complicating factor in many other intractable and difficult-to-treat conditions as well, including cardiovascular diseases, cerebrovascular diseases, respiratory diseases, skin and soft tissue diseases, and neurodegenerative diseases. In addition to our oncology programs past and present, we have previously conducted a variety of preclinical and clinical studies evaluating the effects of TSC in several of these other indications complicated by hypoxia, including COVID-19, stroke, and peripheral artery disease with intermittent claudication, and we intend to continue to pursue potential partnering opportunities in non-oncology indications.



Certain medical conditions complicated by hypoxia.

Our Phase 2 COVID-19 Trial

We believe TSC's oxygen-enhancing mechanism of action could potentially provide benefit patients suffering from respiratory indications, such as COVID-19.

In September 2020, we announced the dosing of the first patients in our COVID Trial evaluating TSC in hospitalized COVID-19 patients at the National Institute of Infectious Diseases in Bucharest, Romania. The trial enrolled 24 patients divided into four sequential cohorts of six patients, with each patient in a cohort receiving the same intravenous doses of 0.25 mg/kg, 0.5 mg/kg, 1.0 mg/kg, or 1.5 mg/kg. All patients were administered intravenous doses of TSC every six hours for a minimum of five days and up to 15 days. On February 9, 2021, we completed dosing of the twenty-fourth and final patient in the trial.

The primary endpoint of the COVID Trial was to evaluate the safety and tolerability of TSC administered every six hours for at least five and up to 15 days, a more frequent dosing regimen than had been used in our previous clinical studies. Secondary endpoints included pharmacokinetic measurement of TSC levels after dosing, relative improvements in blood oxygen levels, and certain other clinical parameters related to COVID-19, such as improvement in WHO ordinal scale by day 7 and through day 29, time on oxygen supplementation, and hospital length of stay.

Data from the trial, evaluated by the study's independent safety monitoring committee, indicated TSC was safe and well-tolerated and that no dose-limiting toxicities or serious adverse events were observed among any patients in the study, including those who received the highest dose administered in the trial. Additionally, while the COVID Trial was not designed or powered to evaluate efficacy, the safety monitoring committee also observed that patients receiving the highest dose administered had improved outcomes in the trial's secondary and exploratory endpoints compared to those receiving lower doses. Further, no patients that received TSC required dialysis or developed acute kidney injury, nor were there any reports of pulmonary embolism or deep vein thrombosis. Based on their observations, the safety monitoring committee also recommended the Company consider testing of higher TSC doses and a continuous intravenous infusion in future studies.

Product Development

Research and Development

In recent years, the majority of our research and development expenditures have been directed to the development of TSC. For example, during the year ended December 31, 2021, we incurred approximately $8.5 million in costs related to research and development of our products, a decrease of approximately $0.9 million compared to the year ended December 31, 2020. The majority of these costs were related to the development of TSC and related personnel, including costs associated with the Oxygenation Trials and the COVID Trial, which was completed in February 2021. We expect this trend to continue for the foreseeable future, including planned expenditures related to completion of the remaining Oxygenation Trials, the initiation of the Hypoxic Solid Tumor Program, and other costs associated with the conduct of additional, supportive preclinical studies and general research and development activities related to TSC and any other product candidates we may acquire or in-license in the future.

As a development-stage company, we continuously evaluate opportunities to improve the value of our development pipeline, including potential acquisition and in-licensing opportunities. Our efforts include ongoing evaluation and modification of our development plans intended to maximize the probability of technical, developmental, and regulatory success while enhancing patient and stockholder value. These activities have, and we expect they will continue to be for the foreseeable future, focused on opportunities that are synergistic with our overall corporate strategy to develop novel treatments for the treatment of hypoxia and conditions complicated by hypoxia.

Intellectual Property

We believe that a strong intellectual property portfolio is critical to our success. We are committed to obtaining and maintaining appropriate patent and other protections for our products candidates and other technologies, preserving and protecting our trade secrets and other confidential and proprietary information, and fiercely defending our intellectual property portfolio against any potential infringement by third parties. We attempt to protect our intellectual property through among other things, the filing of applications for patent, trademark, and other appropriate intellectual property protections, the use of confidentiality agreements with consultants, contractors and other third parties, our employee policies regarding confidentiality, invention disclosure, and the assignment of inventions, as well as regular meetings of members of our internal development and legal teams, which contains key members of our management team. We are also committed to operating our business without infringing on the intellectual property of others.

In general, 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, with term adjustments or extensions possible in certain cases based on patent office delays or pursuant to certain administrative and legislative exceptions. 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.

We continue to invest significant time, effort, and resources into the development and maintenance of our patent portfolio. As of December 31, 2021, we owned 17 issued U.S. patents and more than 35 issued non-U.S. patents, and had numerous patent applications pending worldwide including issued patents and applications in major markets such as the U.S., E.U., China, Japan, and India. The normal life (i.e. with no adjustments or extensions) of our key issued patents related to the composition of matter of TSC extends to 2026, with potential patent term extensions to 2031, and the normal life of our patents related to an oral formulation of TSC extends to 2031, with potential patent term extensions to 2036. The normal life of our key issued patents related to methods of use of TSC extends to 2037, not including potential patent term extensions. For additional information regarding patent term extensions, see "*Business — Government Regulation— The Hatch-Waxman Amendments — Patent Term Restoration and Marketing Exclusivity* . In addition, TSC has been granted Orphan Drug designation by the FDA for the treatment of both GBM and metastatic brain cancer, which may provide us with a right of exclusivity under certain FDA regulations. For additional information regarding orphan and ultra-orphan designations, see "*Business — Government Regulation — Certain Other FDA Regulations — The Orphan Drug Act of 1983*."

Chemistry, Manufacturing, and Controls

TSC is currently formulated as a freeze-dried, injectable product, requiring a sophisticated manufacturing process.

We do not currently own or operate any facilities suitable for manufacturing TSC or any of our other product candidates on a scale required to support either clinical development or commercialization. We currently use third-party CMOs to manufacture API, other starting materials, and finished drug product for our preclinical studies and clinical trials and we intend to continue doing so for the foreseeable future. We anticipate this strategy will be scalable in a manner sufficient to support the production capacity required to support continued clinical development and ultimate commercialization. However, we do not have any formal agreements at this time with any CMO to cover commercial production of TSC or any other product candidate. Although the use of third party CMOs to manufacture pharmaceutical products is common within the industry, this dependence on third-party CMOs exposes our business to certain risks, including those described under the heading, "Risk Factors – Risks Related to Our Dependence on Third Parties."

Supply Chain Matters

Recently, many companies across a variety of sectors have reported disruptions, shortages, and other supply chain-related issues. In the biopharmaceutical sector, delays and interruptions in the supply chain were particularly pronounced as CMOs redirected resources under the Defense Production Act and to otherwise support the COVID-19 vaccine roll-out across the globe.

During 2021, we were able to effectively manage our supply of TSC and its component materials in a manner that avoided any significant interruptions to our clinical programs. We also took actions designed to increase the robustness of our drug supply and overall supply chain to mitigate risks related to the availability of our drug supply in the future. However, as constraints on the supply chain continue to impact the cost and general availability of manufacturing materials, related delays and shortages could affect the cost and timing of our available clinical study drug supply of TSC.

Competition

Currently, medical options to improve oxygenation without risk of hyper-oxygenation are limited and we believe that TSC's diffusion enhancing mechanism of action make it a first-in-class, novel, small molecule. However, there are several companies currently developing or marketing oxygen enhancing products, therapeutics, or devices that may nevertheless be competitive with TSC, if approved, including Hemoglobin Oxygen Therapeutics LLC, Hemotek Medical Inc., NuvOx Pharma LLC, Omniox, Inc., and VirTech Bio Inc. In addition, in the first quarter of 2021, we became aware of a third party affiliated with a former outside consultant of the Company which claims to be in early-stage development of a product candidate that purportedly may operate through a similar mechanism of action to TSC. It is unclear if this Company's product candidate would, if developed and approved, actually be competitive with TSC.

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, smaller biopharmaceutical companies, research universities, and others. The biopharmaceutical and pharmaceutical industries are 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. 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. In addition, 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. One or more of these companies or other entities may have one or more products under development that would be competitive with TSC.

Sales and Marketing

We currently have no marketed products and, accordingly, currently have no sales or marketing personnel.

Government Regulation

Pharmaceuticals like TSC and other product candidates we may develop are highly regulated by governmental authorities in the U.S. and other countries at the federal, state, and local levels. These regulations are numerous and extensive in their scope, relating to, among other things, the research and development, manufacture, storage, quality control and testing, approval, labeling and packaging, promotion, marketing, and advertising, distribution, post-approval monitoring and reporting, export and import, and record keeping of pharmaceutical products.

The FDA Drug Approval Process

Generally, before a new pharmaceutical product can be marketed, considerable data demonstrating its quality, safety and efficacy must be obtained, organized into a format specific for each applicable regulatory authority, submitted for review, and approved by the competent regulatory authority. In the United States, the competent regulatory authority is the FDA, which, pursuant to the FDC Act, is responsible for the review and approval of all data required to support a license to commercially market pharmaceuticals such as TSC.

The process of obtaining regulatory approvals and the subsequent compliance with FDA regulations requires the expenditure of substantial time and financial resources and failure to comply with the applicable requirements at any time during the product development process, approval process, or, if approved, following approval may subject an applicant to administrative or judicial sanctions. These sanctions could include, among other actions, the FDA's refusal to approve pending applications, withdrawal of an approval, license revocation, a clinical hold, untitled or warning letters, voluntary or mandatory product recalls, market withdrawals, product seizures, total or partial suspension of production or distribution, injunctions, fines, refusals of government contracts, restitution, disgorgement and civil or criminal penalties, any of which could have a material adverse effect on our business, financial position, or results of operations.

Process Overview

The FDA drug approval process generally involves the following steps:

- completion of extensive preclinical laboratory studies , including studies conducted in accordance with GLP requirements;
- submission to the FDA of an IND application, which must become effective before clinical trials involving human subjects or patients may begin;
- performance of adequate and well-controlled human clinical trials in accordance with applicable IND regulations, GCP requirements, and other clinical trial-related regulations to establish the safety and efficacy of the investigational product for each proposed indication, including approval by an IRB or independent ethics committee before each trial may be initiated;
- submission to the FDA of an NDA;
- a determination by the FDA within 60 days of its receipt of an NDA as to whether it will accept the filing for review;
- satisfactory completion of one or more FDA pre-approval inspections of the manufacturing facility or facilities where the drug will be produced to assess compliance with cGMP requirements and to assure that the facilities, methods and controls are adequate to preserve the drug's identity, strength, quality and purity;
- a potential FDA audit of the clinical trial sites that generated the data in support of the NDA;
- payment of user fees for FDA review of the NDA; and
- FDA review and approval of the NDA, including consideration of the views of any FDA advisory committee, prior to any commercial marketing or sale of the biologic or drug in the United States.

The preclinical and clinical testing and approval process requires substantial time, effort, and financial resources and satisfaction of FDA pre-market approval requirements typically takes many years, though the actual time required may vary substantially based upon the type, complexity, and novelty of the applicable product or indication to be treated. We cannot be certain that any approvals for TSC or any product candidates we attempt to develop in the future will be granted on a timely basis or at all.

Preclinical Studies

Preclinical studies 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 drug. The results of preclinical testing are submitted to the FDA as part of an IND along with other information related to the drug, including information regarding its chemical make-up, manufacturing process, and quality controls, as well as 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.

Clinical Trials

Following completion of preclinical studies and the submission on an IND to the FDA, a 30-day waiting period is required. 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 an investigational new drug to healthy volunteers or patients under the supervision of a qualified investigator. These trials must be conducted in compliance with federal regulations as well as 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. Each trial is conducted under a protocol 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.

Clinical trials to support NDAs for marketing approval are typically conducted in three sequential phases, but the phases may overlap, especially in certain indications such as cancer.

- Phase 1 - In Phase 1 trials, an investigational new drug is introduced into healthy human subjects and is evaluated to assess pharmacological actions, side effects associated with increasing doses and, in certain cases, early evidence on efficacy.
- Phase 2 - In Phase 2 trials, the drug is introduced to a limited patient population in a particular indication to determine metabolism, pharmacokinetics, the effectiveness of the drug for the indication, dosage tolerance and optimum dosage, and to identify potential adverse effects and safety risks.
- Phase 3 - In Phase 3 trials, if a drug has demonstrated evidence of effectiveness and an acceptable safety profile in prior Phase 2 trials, the drug is introduced to a larger patient population in the relevant indication 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, if approved.

Not all drug development programs are required to follow the order and content of all three phases. For example, in August 2018, the FDA released a draft guidance entitled “Expansion Cohorts: Use in First-In-Human Clinical Trials to Expedite Development of Oncology Drugs and Biologics,” which outlines how drug developers can utilize an adaptive trial design commonly referred to as a seamless trial design in early stages of oncology drug development, i.e., the first-in-human clinical trial, to compress the traditional three phases of trials into one continuous trial called an expansion cohort trial. Information to support the design of individual expansion cohorts is included in IND applications and assessed by FDA. Expansion cohort trials can potentially bring efficiency to drug development and reduce developmental costs and time.

Post-approval trials, sometimes referred to as Phase 4 clinical trials, may be conducted after initial marketing approval. These trials are used to gain additional experience from the treatment of patients in the intended therapeutic indication and are commonly intended to generate additional safety data regarding use of the product in a clinical setting. In certain instances, the FDA may mandate the performance of Phase 4 clinical trials as a condition of approval of an NDA.

Progress reports detailing the results of the clinical trials, among other information, must be submitted at least annually to the FDA and written IND safety reports must be submitted to the FDA and the investigators 15 calendar days after the trial sponsor determines the information qualifies for reporting for serious and unexpected suspected adverse events, findings from other studies or animal or in vitro testing that suggest a significant risk for human subjects and any clinically important increase in the rate of a serious suspected adverse reaction over that listed in the protocol or investigator brochure. The sponsor also must notify the FDA of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible but in no case later than seven calendar days after the sponsor's initial receipt of the information.

Phase 1, Phase 2, Phase 3, and other types of clinical trials may not be completed successfully within any specified period, if at all. The FDA or the sponsor may suspend or terminate a clinical trial at any time on various grounds, including a finding that the patients are being exposed to an unacceptable health risk.

New Drug Application and FDA Review Process

After completion of the required clinical testing, an NDA is prepared and submitted to the FDA containing data intended to provide substantial evidence that the drug is safe and effective in the relevant indication, and FDA approval of the NDA is required before commercial 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, manufacturing, and controls. The cost of preparing and submitting an NDA is substantial, and the submission of most NDAs is also subject to substantial initial and ongoing fees.

The FDA has 60 days from its receipt of an NDA to determine whether the NDA 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 subject to certain performance goals agreed upon by the FDA. Priority review can be applied in certain instances, including with respect to drugs that the FDA determines offer major advances in treatment or provide a treatment where no adequate therapy exists. The review process, whether standard or priority, may be extended by the FDA for three additional months to consider certain late-submitted information or information intended to clarify information already provided in the submission.

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 facilities at which the drug is manufactured to confirm compliance with cGMP. 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. This advisory committee is typically a panel that includes clinicians and other experts in the relevant indication or subject matter who review and evaluate the NDA and provide a recommendation to the FDA 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.

After the FDA evaluates the NDA, the clinical sites, the manufacturing facilities, and, as needed, receives a recommendation from the advisory committee, 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. The FDA has committed to reviewing such resubmissions in two to six months depending on the type of new information included.

FDA Approval Letter

An FDA approval letter authorizes commercial marketing of the drug with specific prescribing information for specific indications. Moreover, product approval may require substantial post-approval testing and surveillance to monitor the drug's safety or efficacy including, in certain cases, REMS as described in more detail under the heading "*—Certain Other FDA Regulations – Risk Evaluation and Mitigation Strategies*." Once granted, product approvals may be withdrawn if compliance with regulatory standards is not maintained or problems are identified following initial marketing.

Further, 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 similar procedures and actions in reviewing NDA supplements as it does in reviewing NDAs.

The Hatch-Waxman Amendments

The Drug Price Competition and Patent Term Restoration Act, commonly referred to as the Hatch-Waxman Amendments, is a 1984 U.S. federal law which established the modern system of generic drug regulation in the U.S. The Hatch-Waxman Amendments were enacted to encourage the manufacture of generic drugs by outlining the process for generic pharmaceutical manufacturers to file an abbreviated new drug application and to provide certain related protections to drug development innovators, namely a new kind of market exclusivity period and the ability to potentially extend patent life by a portion of the time a drug is under regulatory review by the FDA.

Orange Book Listing and Abbreviated New Drug Applications

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 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.

An ANDA applicant is required to make certain certifications to the FDA concerning any such patents listed in the Orange Book for the approved reference drug intended to confirm that the proposed generic equivalent will not infringe on any intellectual property related to the reference drug, commonly referred to as a Paragraph IV certification. The ANDA process gives the owner of the reference drug an opportunity to assert a patent infringement claim if it believes its intellectual property rights are being infringed upon following the submission of a Paragraph IV certification.

An ANDA will not be approved until all patents and non-patent exclusivity periods listed in the Orange Book for the reference drug have expired.

Patent Term Restoration and Marketing Exclusivity

Certain of our current and future product candidates, including TSC, may be eligible for patent term restoration and marketing exclusivity under the Hatch-Waxman Amendment.

The Hatch-Waxman Amendments permit restoration of the patent term of up to five years as compensation for patent term lost during product development and the FDA regulatory review process. Patent term restoration, however, cannot extend the remaining term of a patent beyond a total of 14 years from the product's approval date. The patent term restoration period is generally 50% of the amount of time between the effective date of an IND and the submission date of an NDA, plus the time between the submission date of an NDA and the approval of that application, except that the review period is reduced by any time during which the applicant failed to exercise due diligence. Only one patent applicable to an approved drug is eligible for such an extension and the application for the extension must be submitted prior to the expiration of the patent. The USPTO, in consultation with the FDA, reviews and approves the application for any patent term extension or restoration.

Marketing exclusivity provisions under the FDC Act can also delay the submission or the approval of certain marketing applications. The FDC Act provides three years of marketing exclusivity for an NDA, or supplement to an existing NDA, if new clinical investigations, other than bioavailability studies, that were conducted or sponsored by the applicant are deemed by the FDA to be essential to the approval of the application, for example investigations related to new indications, dosages, or strengths of an existing drug. This three-year exclusivity covers only the modification for which the drug received approval on the basis of the new clinical investigations and does not prohibit the FDA from approving ANDAs for drugs containing the active agent for the original indication or condition of use. The FDC Act also provides a five-year period of non-patent marketing exclusivity within the United States to the first applicant to obtain approval of an NDA for a new chemical entity, meaning the FDA has not previously approved any other new drug containing the same active moiety, which is the molecule or ion responsible for the action of the drug substance.

During the exclusivity period, the FDA may not accept for review an ANDA or a 505(b)(2) NDA submitted by another company for another drug based on the same active moiety, regardless of whether the drug is intended for the same indication as the original innovator drug or for another indication, where the applicant does not own or have a legal right of reference to all the data required for approval. However, an application may be submitted after four years if it contains a certification of patent invalidity or non-infringement to one of the patents listed with the FDA by the innovator NDA holder. Three-year and five-year exclusivity will not delay the submission or approval of a full NDA. However, an applicant submitting a full NDA would be required to conduct or obtain a right of reference to all of the nonclinical studies and adequate and well-controlled clinical trials necessary to demonstrate safety and efficacy.

Certain Other FDA Regulations

The Orphan Drug Act of 1983

Under the Orphan Drug Act, the FDA may grant orphan designation to a drug product intended to treat a rare disease or condition, which is generally a disease or condition that affects fewer than 200,000 individuals in the United States, or more than 200,000 individuals in the United States and for which there is no reasonable expectation that the cost of developing and making the product available in the United States for this type of disease or condition will be recovered from sales of the product. Our lead product candidate, TSC, has been granted Orphan Drug designations by the FDA for the treatment of both GBM and metastatic brain cancer.

Orphan drug designation must be requested before submitting an NDA. After the FDA grants orphan drug designation, the identity of the therapeutic agent and its potential orphan use are disclosed publicly by the FDA. For example, we previously announced that TSC was granted orphan drug designation by the FDA for the treatment of GBM and metastatic brain cancer in July 2011 and in December 2012, respectively. However, orphan drug designation on its own does not convey any advantage in or shorten the duration of the regulatory review and approval process but may result in certain financial and marketing incentives if approved.

If a product that has orphan designation subsequently receives the first FDA approval for the disease or condition for which it has such designation, the product is entitled to orphan drug exclusivity, which means that the FDA may not approve any other applications to market the same drug for the same indication for seven years from the date of such approval, except in limited circumstances, such as a showing of clinical superiority to the product with orphan exclusivity by means of greater effectiveness, greater safety, or providing a major contribution to patient care, or in instances of drug supply issues. Competitors, however, may receive approval of either a different product for the same indication or the same product for a different indication. In the latter case, because health care professionals are free to prescribe products for off-label uses, the competitor's product could be used for the orphan indication despite our orphan exclusivity. Orphan drug exclusivity could also block the approval of one of our products for seven years if a competitor obtains approval before we do for the same drug and same indication, as defined by the FDA, for which we are seeking approval, or if our product is determined to be contained within the scope of the competitor's product for the same indication or disease. If we pursue marketing approval for an indication broader than the orphan drug designation we have received, we may not be entitled to orphan drug exclusivity. Orphan drug status in the E.U. has similar, but not identical, requirements and benefits.

Expedited Development and Review Programs

The FDA has a fast track program that is intended to expedite or facilitate the process for reviewing new drugs that meet certain criteria. Specifically, new drugs are eligible for fast track designation if they are intended to treat a serious or life-threatening condition and preclinical or clinical data demonstrate the potential to address unmet medical needs for the condition. Fast track designation applies to both the product and the specific indication for which it is being studied. The sponsor can request the FDA to designate the product for fast track status any time before receiving NDA approval, but ideally no later than the pre-NDA meeting. Any product submitted to the FDA for marketing, including under a fast track program, may be eligible for other types of FDA programs intended to expedite development and review, such as priority review and accelerated approval. Any product is eligible for priority review if it treats a serious or life-threatening condition and, if approved, would provide a significant improvement in safety and effectiveness compared to available therapies. The FDA will attempt to direct additional resources to the evaluation of an application for a new drug designated for priority review in an effort to facilitate the review.

A product may also be eligible for accelerated approval, if it treats a serious or life-threatening condition and generally provides a meaningful advantage over available therapies. In addition, it must demonstrate an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit or on a clinical endpoint that can be measured earlier than IMM that is reasonably likely to predict an effect on IMM or other clinical benefit. As a condition of approval, the FDA may require that a sponsor of a drug receiving accelerated approval perform adequate and well-controlled post-marketing clinical trials. If the FDA concludes that a drug shown to be effective can be safely used only if distribution or use is restricted, it will require such post-marketing restrictions, as it deems necessary to assure safe use of the product. If the FDA determines that the conditions of approval are not being met, the FDA can withdraw its accelerated approval for such drug.

Additionally, a drug may be eligible for designation as a breakthrough therapy if the product is intended, alone or in combination with one or more other drugs, to treat a serious or life-threatening condition and preliminary clinical evidence indicates that the product may demonstrate substantial improvement over currently approved therapies on one or more clinically significant endpoints. The benefits of breakthrough therapy designation include the same benefits as fast track designation, plus intensive guidance from the FDA to ensure an efficient drug development program.

Even if a product qualifies for one or more of these programs, the FDA may later decide that the product no longer meets the conditions for qualification or the time period for FDA review or approval may not be shortened. Furthermore, fast track designation, priority review, accelerated approval, and breakthrough therapy designation do not change the standards for approval, but may expedite the development or approval process.

Rare Pediatric Disease Priority Review Voucher Program

In 2012, Congress authorized the FDA to award priority review vouchers to sponsors of certain rare pediatric disease product applications. This program is designed to encourage development of new drug and biological products for prevention and treatment of certain rare pediatric diseases. Specifically, under this program, a sponsor who receives an approval for a drug or biologic for a "rare pediatric disease" may qualify for a voucher that can be redeemed to receive a priority review of a subsequent marketing application for a different product. The sponsor of a rare pediatric disease drug product receiving a priority review voucher may transfer (including by sale) the voucher to another sponsor. The voucher may be further transferred any number of times before the voucher is used, as long as the sponsor making the transfer has not yet submitted the application. The FDA may also revoke any priority review voucher if the rare pediatric disease drug for which the voucher was awarded is not marketed in the U.S. within one year following the date of approval.

For purposes of this program, a "rare pediatric disease" is a (a) serious or life-threatening disease in which the serious or life-threatening manifestations primarily affect individuals aged from birth to 18 years, including age groups often called neonates, infants, children, and adolescents; and (b) a rare disease or condition within the meaning of the Orphan Drug Act. On December 27, 2020, the Rare Pediatric Disease Priority Review Voucher Program was extended. Under the current statutory sunset provisions, after September 30, 2024, FDA may only award a voucher for an approved rare pediatric disease product application if the sponsor has rare pediatric disease designation for the drug, and that designation was granted by September 30, 2024. After September 30, 2026, FDA may not award any Rare Pediatric Disease Priority Review Voucher.

Disclosure of Clinical Trial Information

Sponsors of clinical trials of FDA-regulated products are required to register and disclose to the public certain clinical trial information, including information related to the product, patient population, phase of investigation, study sites, investigators, and other aspects of the trial design. Sponsors are also obligated to discuss the results of their clinical trials after completion. However, disclosure of the results of these trials can be delayed until the new product or new indication being studied has been approved as competitors may otherwise use this or other publicly-available information to gain knowledge regarding the progress of development programs and gain a competitive advantage.

Risk Evaluation and Mitigation Strategies and Other Post-Approval Requirements

As a condition of NDA approval, the FDA may require a REMS to help ensure that the benefits of the drug's continued approval outweigh the potential risks. 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. REMS can include medication guides, communication plans for healthcare professionals, and elements to assure safe use. Elements to assure safe use can include, but are not limited to, special training or certification for prescribing or dispensing, dispensing only under certain circumstances, special monitoring requirements, and the use of patient registries. The requirement for a REMS can materially affect the potential market and profitability of a drug product.

Even if the FDA does not require a REMS, once an NDA is approved, a product will be subject to certain post-approval regulations. 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. Adverse event reporting and the submission of periodic reports are also required following FDA approval of an NDA.

Drug Approval Process and Other Regulations Outside of the U.S.

In addition to regulations in the U.S., we are and will be subject to the regulations of other countries in which we conduct any of our clinical trials or engage in commercial sales or other distribution of our products, if approved. Whether or not we obtain FDA approval for conduct of a clinical trial or distribution of a product, we must obtain approval from the competent regulatory authority of any country or economic area in which we would seek to commence a clinical trial or market products. For example, conduct of the COVID Trial in Bucharest, Romania, required certain approvals from regulatory authorities in Romania and the E.U. Certain countries outside of the United States have a process similar to the FDA's IND process which requires the submission of a CTA prior to the commencement of human clinical trials. In the E.U., for example, a CTA must be submitted to each country's national health authority and an independent ethics committee, which operates similar to an IRB under U.S. regulations. Once the CTA is approved in accordance with a country's requirements, the clinical trial may proceed in the applicable country. 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.

In particular, in the E.U. a company may submit marketing authorization applications (comparable to an NDA submission in the US to the FDA) under either 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 medicines which are highly innovative, provides for the grant of a single marketing authorization that is valid for all E.U. member states. The decentralized procedure provides for mutual recognition of national approval decisions. Under this decentralized procedure, the holder of a national marketing authorization in any E.U. member state may submit an application to the remaining member states. Within ninety 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. The E.U. also has procedures similar to those of the FDA pursuant to which a company may obtain marketing exclusivity for a product for up to 11 years and/or orphan drug designation and related exclusivity for up to ten years, as well as other expedited approval pathways available to certain drugs.

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 E.U. 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 E.U. do not follow price structures of the U.S. and generally tend to be significantly lower.

Certain Other Legislation and Regulations

Current Healthcare Laws and Regulations

Healthcare providers, physicians, and third party payors, including governmental payors such as Medicare and Medicaid, will play a significant role in the recommendation and prescription of any products for which we obtain marketing approval. Our future arrangements with third party payors, healthcare providers, and physicians may expose us to broadly applicable fraud and abuse and other healthcare laws and regulations that may constrain the business or financial arrangements and relationships through which we market, sell, and distribute any drugs for which we obtain marketing approval.

These laws include, without limitation, state and federal anti-kickback, false claims, physician transparency, and patient data privacy and security laws and regulations, and other federal, state, and local regulations and legislation impacting the pharmaceutical and biopharmaceutical industries, including but not limited to those described below.

- Health Insurance Portability and Accountability Act - HIPAA imposes criminal and civil liability for, among other things, knowingly and willfully executing a scheme, or attempting to execute a scheme, to defraud any healthcare benefit program, including private payors, or falsifying, concealing, or covering up a material fact or making any materially false statements in connection with the delivery of or payment for healthcare benefits, items or services. Similar to the federal Anti-Kickback Statute, a person or entity does not need to have actual knowledge of the statute or specific intent to violate it in order to have committed a violation. HIPAA, as amended by HITECH and their respective implementing regulations, imposes, among other things, specified requirements on covered entities and their business associates relating to the privacy and security of individually identifiable health information, including mandatory contractual terms and required implementation of technical safeguards of such information. HITECH also created new tiers of civil monetary penalties, amended HIPAA to make civil and criminal penalties directly applicable to business associates, and gave state Attorneys General new authority to file civil actions for damages or injunctions in federal courts to enforce the federal HIPAA laws and seek attorneys' fees and costs associated with pursuing federal civil actions.

- Affordable Care Act - The ACA was enacted in March 2010 and included measures intended to significantly change the way healthcare is financed in the U.S. by both governmental and private insurers which have and may continue to impact the pharmaceutical and biopharmaceutical industries, including expanded Medicare and Medicaid benefits, expansion of healthcare fraud and abuse laws, establishment of the CMS, annual reporting requirements for manufacturers and distributors. Since its enactment, there have been numerous judicial, administrative, executive, and legislative challenges to certain aspects of the Affordable Care Act, and we expect there will be additional challenges and amendments to the ACA in the future. In addition, subsequent legislation, including the Budget Control Act of 2011, American Taxpayer Relief Act of 2012, and Coronavirus Aid, Relief, and Economic Security Act of 2020, has limited and supplemented various provisions of the Affordable Care Act. While we cannot predict what effect further changes to the Affordable Care Act would have on our business, the Affordable Care Act is likely to continue to impact the regulatory regime to which we are subject for the foreseeable future, and we cannot predict the ultimate content, timing, or effect of any healthcare reform legislation or the impact of potential legislation on us.

- 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 that may impact our business, 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 and compassionate use programs, and clarifying how manufacturers communicate about their products.

- Anti-Kickback Laws - The federal Anti-Kickback Statute makes it illegal for any person, including a prescription drug manufacturer (or a party acting on its behalf), to knowingly and willfully solicit, receive, offer, or pay any remuneration, directly or indirectly, in cash or in kind, that is intended to induce or reward referrals, including the purchase, recommendation, order or prescription of a particular drug or any other good or service, for which payment may be made under a federal healthcare program, such as Medicare or Medicaid. Violations of this law are punishable by up to five years in prison, criminal fines, administrative civil money penalties, and exclusion from participation in federal healthcare programs. In addition, a person or entity does not need to have actual knowledge of the statute or specific intent to violate it.

- False Claims Laws - The federal False Claims Act imposes civil penalties, including through civil whistleblower or qui tam actions, against individuals or entities (including manufacturers) for, among other things, knowingly presenting, or causing to be presented, false or fraudulent claims for payment by a federal healthcare program or making a false statement or record material to payment of a false claim or avoiding, decreasing, or concealing an obligation to pay money to the federal government. The government may deem manufacturers to have “caused” the submission of false or fraudulent claims by, for example, providing inaccurate billing or coding information to customers or promoting a product off-label.

- Medicare Prescription Drug, Improvement, and Modernization Act - The Medicare Prescription Drug, Improvement, and Modernization Act of 2003 imposes requirements on 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, but 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 reduction in payment that results from the these or similar regulations may result in a similar reduction in payments from non-governmental payors.

- The Physician Payments Sunshine Act - The Sunshine Act, enacted as part of the Affordable Care Act,, imposed new annual reporting requirements for certain manufacturers of drugs, devices, biologics, and medical supplies for which payment is available under Medicare, Medicaid, or the Children's Health Insurance Program, for certain payments and "transfers of value" provided to physicians (defined to include doctors, dentists, optometrists, podiatrists and chiropractors) and teaching hospitals, as well as ownership and investment interests held by physicians and their immediate family members. Effective January 1, 2022, these reporting obligations will extend to include transfers of value made to certain non-physician providers such as physician assistants and nurse practitioners.

- State, Local, and Non-U.S. Legislation and Regulations - In addition, to the legislation summarized above, we may also be subject now or in the future to analogous state, local, and non-U.S. laws and regulations, such as state anti-kickback and false claims laws, which may be broader in scope and apply regardless of payor. Such laws are enforced by various state agencies and through private actions. For example, some state laws require pharmaceutical companies to comply with the pharmaceutical industry's voluntary compliance guidelines and the relevant federal government compliance guidance, require drug manufacturers to report information related to payments and other transfers of value to physicians and other healthcare providers, and restrict marketing practices or require disclosure of marketing expenditures. Certain state and foreign laws also govern the privacy and security of health information in some circumstances and these data privacy and security laws may differ from both HIPAA and each other in significant ways, which would potentially increase our compliance burden.

The scope and enforcement of each of these laws is uncertain and subject to rapid change in the current environment of healthcare reform. Federal and state enforcement bodies have recently increased their scrutiny of interactions between healthcare companies and healthcare providers, which has led to a number of investigations, prosecutions, convictions, and settlements in the healthcare industry. If our operations are found to be in violation of any of these laws or any other related governmental regulations that may apply to us, we may be subject to significant civil, criminal, and administrative penalties, damages, fines, imprisonment, disgorgement, exclusion of drugs from government funded healthcare programs, such as Medicare and Medicaid, reputational harm, additional oversight, and reporting obligations if we become subject to a corporate integrity agreement or similar settlement to resolve allegations of non-compliance with these laws and the curtailment or restructuring of our operations.

Future Healthcare Laws and Regulations

In the United States and foreign jurisdictions, there have been a number of proposed changes regarding the healthcare system and its regulation that could prevent or delay marketing approval of our product candidates, restrict or regulate post-approval activities, and affect our ability to profitably sell any product candidates for which we obtain marketing approval. We expect that further implementation of current laws, as well as other healthcare reform measures that may be adopted in the future, may result in more rigorous coverage criteria and in additional downward pressure on the price that we, or any strategic collaborators, may receive for any approved products. Further, there has recently been heightened governmental scrutiny over the manner in which manufacturers set prices for their marketed products, which have resulted in several recent Congressional inquiries and proposed bills designed to, among other things, bring more transparency to product pricing, review the relationship between pricing and manufacturer patient programs, and reform government program reimbursement methodologies for products.

U.S. Environmental, Health, and Safety Laws

We are subject to numerous environmental, health, and safety laws and regulations. From time to time and in the future, our operations may involve the use of hazardous and flammable materials, including chemicals and biological materials, and may also produce hazardous waste products. Even if we contract with third parties for the disposal of these materials and waste products, we cannot completely eliminate the risk of contamination or injury resulting from these materials. In the event of contamination or injury resulting from the use or disposal of our hazardous materials, we could be held liable for any resulting damages, and any liability could exceed our resources. We also could incur significant costs associated with civil or criminal fines and penalties for failure to comply with such laws and regulations.

In addition, we may incur substantial costs in order to comply with current or future environmental, health, and safety laws and regulations. Current or future environmental laws and regulations may impair our research, development or production efforts. In addition, failure to comply with these laws and regulations may result in substantial fines, penalties or other sanctions.

Public Company Status

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 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.

Our People and Human Capital Resources

As of December 31, 2021, we had 16 full-time employees, up from 12 employees as of December 31, 2020. We also regularly work with several independent consultants and other contract organizations to support our business and we regularly evaluate additional talent to help support our product manufacturing, development, financial, and other capabilities.

Diversity and Inclusion

We believe that an inclusive culture is required to understand and develop products that benefit all patients. By embracing differences, we aim to foster an environment of respect and trust in an effort to facilitate creativity, spark passion, and help us achieve better outcomes for all those who work at and with Diffusion. We are committed to creating and maintaining a workplace free from discrimination or harassment, including on the basis of any class protected by applicable law, and our recruitment, hiring, development, training, compensation, and advancement practices are based on qualifications, performance, skills, and experience without regard to gender, race, or ethnicity. Our management team and employees are expected to exhibit and promote honest, ethical, and respectful conduct in the workplace, including adhering to the standards for appropriate behavior set forth in our code of conduct.

Compensation and Benefits

We operate in a highly competitive environment for human capital, particularly as we seek to attract and retain talent with relevant experience in the biotechnology and pharmaceutical sectors. Therefore, we strive to provide a total rewards package to our employees that is competitive with our peer companies, including competitive pay, a comprehensive healthcare benefits package (including an 80% employer contribution to family medical coverage), 25 days of paid leave, a company-sponsored 401(k) savings plan, short-term and long-term disability, and other benefits, as well as remote working and flexible work schedules. We also offer every full-time employee the benefit of equity ownership in Diffusion through stock option grants. We believe these grants both help promote alignment between our employees and our stockholders and provide retention benefits, as the awards generally vest over a three-year period.

We do not have any employees that are represented by a labor union or that have entered into a collective bargaining agreement with the Company.

Safety and Wellness

At Diffusion, we believe that health matters to everyone, and the safety health, and wellness of our employees is one of our top priorities. We are committed to developing and fostering a work environment that is safe, professional, and promotes teamwork, diversity, and trust in order to afford all of our employees the opportunity to contribute to the best of their abilities.

Over the past two years, in response to the COVID-19 pandemic, we have taken certain measures and responded to changes in our operational needs, including actions designed to provide a safe work environment for our employees. These actions included investing in technology solutions to support increased work-from-home capabilities, shifting work schedules to reduce the number of people present in our offices, requiring mask wearing and social distancing, making hand sanitizer readily available, and other measures intended to comply with health and safety protocols as required by federal, state, and local governmental agencies, as well as guidance from the U.S. Centers for Disease Control and Prevention and similar public health authorities.

Employee Development and Training

We believe our people are among our most important assets. We focus on attracting, retaining, and cultivating talented individuals and believe in investing in our people to help them grow. Employees are encouraged to attend scientific, clinical, technological, and other relevant meetings and conferences and we strive to provide employees access to a broad set of internal resources intended to help them be successful, including a variety of training and educational materials. During 2021, we intend to implement a new, comprehensive employee evaluation program tied to the achievement of individual, team, and company goals to help further support, retain, and develop our people and further promote alignment of interests between our employees, future target customers, and our stockholders.

Directors and Executive Officers

The information set forth in "*Part III — Item 10 — Directors, Officers, and Corporate Governance*," of this Annual Report is incorporated herein by reference.

Other Information About Our Company

Corporate Information and History

We were originally incorporated under the laws of the State of Nevada on January 10, 1995 and reincorporated under the laws of the State of Delaware on June 18, 2015 under the name, “RestorGenex Corporation.” On January 8, 2016, we completed the merger of our wholly owned subsidiary with and into Diffusion LLC, which was treated as a "reverse acquisition" under GAAP pursuant to which Diffusion LLC's historical results of operations replaced the Company's for all periods prior to the merger. Immediately following the closing of the merger, we changed our name from "RestorGenex Corporation" to "Diffusion Pharmaceuticals Inc."

On May 6, 2021, we received a written notice from the Nasdaq Staff indicating that we were not in compliance with 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. On November 3, 2021, after failing to regain compliance with the Bid Price Rule within 180 days of our receipt of the first notice, we received an additional notice from the Staff providing that, although the Company had not regained compliance with the Bid Price Rule by the previously stated deadline, in accordance with Nasdaq Listing Rule 5810(c)(3)(A), the Company would be granted an additional 180 calendar days, or until May 2, 2022, to regain compliance with the Bid Price Rule. As part of our efforts to regain compliance with the Bid Price Rule, on February 28, 2022, we filed a definitive proxy statement related to a special meeting of our stockholders scheduled for Thursday, April 14, 2022 at which our stockholders will vote upon proposal, approved and recommended for stockholder approval by the Board, to amend our Certificate of Incorporation to effect a reverse stock split of our outstanding shares of common stock by a ratio of any whole number between 1-for-2 and 1-for-50 at any time prior to December 31, 2022, the timing and implementation of which will be subject to the discretion of the Board. To regain compliance, the bid price for the Company’s common stock must close at $1.00 per share or more for a minimum of 10 consecutive business days.

Our principal corporate office is located at 300 East Main Street, Suite 201, Charlottesville, Virginia 22902, and our telephone number is (434) 220-0718. Our website, www.diffusionpharma.com, including the Investor Relations section, investors.diffusionpharma.com, and our social media channels – Facebook (www.facebook.com/diffusionpharmaceuticalsinc/), Twitter (www.twitter.com/diffusionpharma) and LinkedIn (https://www.linkedin.com/company/diffusion-pharmaceuticals/) -- contain a significant amount of information about the Company. We encourage investors to visit these websites and social media channels as information is frequently updated and new information is shared. However, the information included on our website and available through our social media channels is not incorporated by reference into, and should not be considered part of, this Annual Report or any other filings we make with the SEC.

Available Information

We make available on or through our website certain reports that we file with or furnish to the SEC in accordance with Exchange Act. These include our Annual Reports on Form 10-K, our Quarterly Reports on Form 10-Q, and our Current Reports on Form 8-K, as well as any amendments to those reports, filed or furnished pursuant to Section 13(a) or 15(d) of the Exchange Act. We make this information available free of charge as soon as reasonably practicable after we electronically file the information with, or furnish it to, the SEC. The SEC also maintains a website, www.sec.gov, that contains reports, proxy and information statements, and other information regarding the Company and other issuers that file electronically with the SEC. We also make available, free of charge and through our website, the charters of the committees of the Board, our Corporate Governance Guidelines, and our Code of Business Conduct and Ethics.

ITEM 1A. RISK FACTORS

Investing in our common stock involves a high degree of risk. Set forth below are certain material risks and uncertainties known to us that could adversely affect our business, financial condition, or results of operations or could cause our actual results to differ materially from our expectations expressed elsewhere in this Annual Report. The occurrence of the events contemplated by one or more of the factors we describe below could cause the market price of our common stock to decline, resulting in the loss of all or part of any investment in our common stock. Furthermore, other risks that are currently unknown to us or that we currently believe to be immaterial may also, nevertheless, adversely affect our business, financial condition, or results of operations in a way that is material.

Before investing in our common stock, you should carefully consider these risks and uncertainties, together with all other information in this Annual Report, including our consolidated financial statements and related notes, the information included in, *Part II — Item 7 — Management's Discussion and Analysis of Financial Condition and Results of Operations,* and the information incorporated herein by reference.

Risks Related to the Development, Regulatory Approval, and Commercialization of TSC and Our Other Product Candidates

The success of Diffusion is dependent on the successful development, regulatory approval, and, ultimately, commercialization of TSC and our other product candidates. However, the drug development process is expensive, time-consuming and uncertain. Our efforts to develop, obtain regulatory approval for, and commercialize TSC or any other product candidate could fail at any stage of the development process for a variety of reasons, including the possibility that TSC fails to adequately demonstrate efficacy or proof of concept in the Oxygenation Trials. Furthermore, because the results of preclinical studies and early-stage clinical trials are not necessarily predictive of future results, even if we are able to advance TSC or another product candidate into additional clinical trials – for example, beyond our Planned Phase 2 Hypoxic Solid Tumor Trial – we may not continue to experience favorable results.

The success of Diffusion, including our ability to finance our operations and generate revenue in the future, will depend primarily on the successful development, regulatory approval, and, ultimately, commercialization of our product candidates. Currently, the majority of our product development resources are dedicated to our lead product candidate, TSC. In the future, we may also seek to develop or commercialize additional product candidates, including product candidates that we may in-license or acquire to supplement our internally developed portfolio.

The drug development process is very expensive, time-consuming, difficult to design and implement, and its outcome is inherently uncertain. Most product candidates that commence clinical trials are never approved by regulatory authorities for commercialization and success in early-stage clinical trials does not ensure that later clinical trials will demonstrate the efficacy and safety of an investigational drug in a manner adequate to support regulatory approval. Countless other companies, including many with greater resources and experience, have failed or suffered significant setbacks attempting to navigate the drug development process, including failed attempts to develop treatments for hypoxia and indications on the hypoxia-continuum that we may ultimately choose to target with TSC, and there can be no assurance that we will have success where others have failed.

Our product candidates, including TSC, remain in early stages of the development process and we expect that the additional clinical trials necessary to support an NDA will take several years to complete. 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. Furthermore, the timeline for our clinical trials may be delayed in the future for a variety of reasons, including delays related to regulatory and IRB review and approval, slower than anticipated rates of enrollment in or early withdrawals from the trial, third party performance issues beyond our control including any CRO engaged in the conduct of the trial, discovery of series or unexpected toxicities or side effects, or a lack of effectiveness.

Whether we are able to successfully develop TSC or any of our other product candidates will depend on a large number of factors, including the following:

- our ability to complete our planned and future clinical trials in a timely manner and, with respect to any future trials beyond the ongoing Oxygenation Trials and our Planned Phase 2 Hypoxic Solid Tumor Trial, our ability to fund such trials;
- our ability to demonstrate safety and efficacy to the satisfaction of the FDA and similar foreign regulatory authorities, and whether we are required by any such body to conduct additional clinical trials to support approval;
- the receipt of necessary regulatory approvals, including acceptance of our proposed indications and primary endpoint assessments, marketing approvals, and labeling claims;
- a continued acceptable safety profile during development and following approval, including the prevalence, duration and severity of potential side effects experienced; and
- our ability to commercialize successfully, including scaling our manufacturing capabilities, the development of sales and marketing capabilities internally or through a third party, acceptance by physicians and patients of the benefits, safety and efficacy of our treatments.

Any of these factors, many of which are beyond our control, could result in significant delays or an inability to develop, obtain regulatory approvals for, or commercialize our product candidates, and we may ultimately be able to receive regulatory approval or generate revenue from the sale of TSC or any other product candidate.

A number of companies in the pharmaceutical and biopharmaceutical industry have suffered significant setbacks in later-stage Phase 3 clinical development even after promising results in earlier preclinical studies or clinical trials. If later-stage clinical trials do not produce favorable results for TSC or any other product candidate, or we are unable to complete the necessary clinical trials for any reason (including a lack of funding), our ability to achieve regulatory approval or successfully commercialize may be compromised. At any time, we may decide or be forced by circumstance to delay or discontinue the development or commercialization of TSC or any of our other product candidates, including as a result of unfavorable results in later-stage clinical trials, changes in our internal product, technology or indication focus, the appearance of new technologies that make our product candidate obsolete, competition from a competing product, or changes in (or failure to comply with) applicable regulatory requirements. If we decide or are forced to terminate the TSC development program or any future program in which we have invested significant resources, we will not receive any return on our investment despite the allocation of significant resources, we may not be able to execute on our business plan effectively, and our business, financial condition, results of operations may be materially and adversely affected.

Even if we are able to successfully complete the clinical trials and over development activities necessary to submit an NDA to the FDA or an application for marketing approval to an equivalent non-U.S. regulatory authority, we may be unable to obtain regulatory approval for TSC or any other product candidates we may attempt to develop in future, for the indications for which we initially seek approval or at all. The FDA and similar non-U.S. regulatory authorities have significant discretion in the approval process, including the ability to delay, limit, or deny approval of product candidates. The delay, limitation, or denial of regulatory approval for any of our product candidates, and TSC in particular, would limit or restrict altogether our ability to commercialize the product and generate revenue, which could materially and adversely impact our business, financial condition, and results of operations.

We currently have no products approved for sale, and we may never obtain regulatory approval to commercialize TSC or any other product candidates we may attempt to develop in the future. 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 drug products are subject to extensive regulation by the FDA and other regulatory authorities in the United States and abroad, which often differ from country to country. We will not be permitted to market TSC or any of our other current product candidates in the U.S. until we receive approval of an NDA or other applicable regulatory filing from the FDA, and we will not be permitted to market TSC or any of our other current product candidates in any non-U.S. countries until we receive the requisite approval from the applicable regulatory authorities.

To gain approval to market a new drug, such as TSC, the FDA and similar non-U.S. regulatory authorities require the submission of an NDA (or similar application) that contains preclinical and clinical data adequately demonstrating the safety, purity, potency, efficacy, and compliant manufacturing of the product for the intended indication. The FDA and their non-U.S. counterparts have substantial discretion in the drug approval process, including the ability to delay, limit, or deny approval of applications for many reasons, including:

- deemed issues with the design or execution of one or more clinical trials;
- deemed deficiencies in the formulation, quality control, labeling, or specifications of the product candidate;
- deemed issues in our manufacturing processes or in the controls or facilities of third-party manufacturers or testing labs with which we contract;
- a determination that the data from preclinical studies and clinical trials included in the application is not sufficient to support approval, or do not meet a required level of statistical or clinical significance, including as a result of a differing interpretation of the data than that presented by the Company in our application;
- a determination that the perceived risks of approving the product candidate outweigh the clinical and other benefits of approval;
- a determination that additional preclinical studies or clinical trials are required, either prior to or as a contingency to approval, and, for certain target indications such as pediatric populations, in the targeted sub-population;
- a determination that a product candidate may only be approved on a contingent basis or for a more limited indication or patient population than we request;
- a determination that labeling we believe is necessary or desirable for successful commercialization cannot be approved; or
- unanticipated future changes to the approval process and related regulations.

Historically, of the large number of drugs in development at any given time, only a small percentage successfully complete the regulatory approval processes and are ultimately commercialized. Our product candidates may not be approved for sale and marketing by the FDA or any other governmental authority, 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 a further phase of clinical development, or may change the requirements for approval even after such agency has reviewed and commented on the design for the clinical trials.

Any delay in obtaining, or inability to obtain, the regulatory approvals necessary to market and sell our product candidates would delay or prevent commercialization and would materially and adversely affect our business, financial condition, and result of operations. Furthermore, if we determine in the future that the development, approval, or commercial prospects of any product candidate are insufficient to justify our continued expenditure of the associated development and other costs, we may choose to delay, suspend, or abandon our development or commercialization efforts with respect thereto, which would reduce or eliminate our potential return on investment for those product candidates.

Our ability to develop our product candidates depends, and, if TSC or any of our other product candidates are approved, our ability to successfully commercialize our products will depend, in part on our ability to successfully obtain sufficient quantities of the necessary APIs, other component substances and materials, and finished drug product for our product candidates. We are currently entirely dependent on third parties for the manufacture and supply of our product candidates and their component parts, including, with respect to TSC, a sole supplier. We may be unable to continue to develop or commercialize our product candidates or face significant delays in that process if we are unable to successfully obtain these materials or manufacture drug product in sufficient quantities.

Maintaining an adequate supply of TSC and our other product candidates to meet our needs is critical to the success of our business. However, manufacturing and supply of APIs, other substances and materials and finished drug products is a complex and technically challenging process, and changes beyond our direct control can impact the quality, volume, price, and successful delivery of our product candidates or impede, delay, limit or prevent the successful development and commercialization of our product candidates. Mistakes and mishandling are not uncommon in the biopharmaceutical and pharmaceutical industry and can affect successful production and supply significantly.

As of the date of this Annual Report, we have no internal manufacturing capabilities and therefore we do not have direct control over our ability to maintain drug supply sufficient to serve our needs for our ongoing and planned clinical trials or, if any of our product candidates are approved, commercialization. Although we are ultimately responsible for ensuring compliance with regulatory requirements such as cGMPs, we are dependent on our third party CMOs and other contract suppliers and manufacturers for the manufacture of our drug product, including both APIs and finished products, as well as day-to-day compliance with cGMPs and certain other manufacturing-related regulatory requirements. 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, provide regulators with certain technical information, and be approved by the FDA and other relevant regulatory authorities to confirm compliance with cGMP requirements and other regulatory requirements. If the safety of TSC or any of our other product candidates (or any component thereof) is found in the future to be compromised, we may not be able to successfully commercialize or obtain regulatory approval for the product candidate, and we may be held liable for injuries sustained as a result.

Any disruption in our relationship with these third parties or their ability to manufacture the APIs and finished drug product we need for our clinical trials and other development activities could result in significant delays in our anticipated development timelines and/or significant additional supply costs. Such a disruption could be the result of any number of reasons, including contractual disputes with our partners, regulatory issues with our partners or at their facilities (whether or not related to Diffusion or our drug product), financial issues faced by our partners (including bankruptcy or insolvency), damages to our partners' facilities or equipment, communication breakdowns, or acts of God. For example, during 2021 we faced certain delays in the manufacturing process for planned, new batches of TSC drug product due to the fact that, in connection with the U.S. federal government's Operation Warp Speed initiative in response to the COVID-19 pandemic, the facility at which our former, primary CMO partner conducts significant portions of the TSC manufacturing process had been mandated to devote the majority of the facility's available resources to the manufacture of components of the COVID-19 vaccine.

Amplifying this risk is the fact that, notwithstanding the improvements made to our supply chain during 2021 described under, "*Business - Product Development - Chemistry, Manufacturing, and Controls,"* we currently depend upon a sole source to manufacture our API for TSC and other aspects of our manufacturing process, limiting our available options to troubleshoot these issues. Although we actively manage this third-party relationship to ensure continuity, quality, and compliance with regulations and we intend to identify and develop alternative manufacturing and supply alternatives in the future, this process remains ongoing, will take time, and will involve significant costs. Even with these efforts, some events beyond our control, including global instability due to political unrest or from an outbreak of pandemic or contagious disease, such as COVID-19, could result in supply chain disruptions or the complete or partial failure of these manufacturing services. Any such failure or disruptions could materially adversely affect our business, financial condition, cash flows, and results of operations. Furthermore, due to the significant regulatory oversight of the pharmaceutical manufacturing process, any changes in the identity of our third-party partners or in our manufacturing processes – even if in the best interests of the Company and successful – could result in regulatory and other delays, as well as significant additional costs. In addition, if our current supplier terminated our arrangement or failed to meet our supply needs for any reason prior to the time we are able to identify sufficient alternative manufacturing capacity, we may be forced to delay our development plans significantly.

Our CMO and other manufacturing and supply partners are also engaged to supply and manufacture materials or products for other biopharmaceutical and pharmaceutical companies, exposing them to regulatory risks unrelated to the work they are doing for Diffusion but which may nevertheless impact their ability to meet their contractual requirements to us or otherwise impede their ability to supply us with sufficient quantities of drug product. 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, even if such lack of approval is unrelated to Diffusion or our product candidates, we may need to find alternative supply or manufacturing facilities.

In addition, to date we have only manufactured TSC and our other product candidates in relatively small quantities for preclinical studies and clinical trials. As we prepare for additional, later-stage clinical trials and potential commercialization, we will need to take steps to substantially increase the scale at which we are able to produce TSC, its API, and its other component parts. In order to meet these needs, our CMOs and suppliers will need to produce our API, other components, and finished product 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. Even if such a scale up is possible, it may require additional processes, technologies, and validation studies, which are costly, may not be successful, and which the FDA and foreign regulatory authorities would need to review and approve prior to any commercial sale of TSC or any other product candidate. In addition, quality issues may arise during those scale-up activities because of the inherent properties of a product candidate itself or in combination with other components added during the process of manufacturing, packaging, shipping, or storage.

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 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.

Any of these factors could cause a delay or termination of preclinical studies, clinical trials, other development activities, regulatory submissions or approvals of our product candidates, or, if any of our product candidates is approved, commercial supply, and could result in significant, unanticipated costs or an inability to effectively develop our products candidates or commercialize our approved products on a timely basis, or at all, which could materially and adversely affect our business, financial condition, and results of operations.

We expect to rely on third-party CROs and other third parties to conduct and oversee our clinical trials and other aspects of our development process for TSC and our other product candidates. If these third parties do not meet our requirements or otherwise conduct the trials or perform the other services for which they are engaged, we may not be able to successfully develop, obtain regulatory approval for, or commercialize our product candidates when expected or at all. Furthermore, if we are not able to establish and maintain the necessary collaborative relationships with our CROs and other third party partners, we may have to alter our development and commercialization plans.

Conducting our clinical trials in a safe, compliant, and timely manner is critical to our success. We currently rely on third-party CROs to conduct and oversee our clinical trials and other aspects of our product development, as well as various medical institutions, clinical investigators, contract laboratories, consultants, and other third parties to design and conduct our trials, to analyze the results therefrom, and to ensure that the trials are conducted in accordance with our clinical protocols and all applicable regulatory requirements, including the FDA's regulations and GCPs. These CROs and other third parties play a significant role in the conduct of these trials and the subsequent collection and analysis of data therefrom, as we control only certain aspects of their activities and rely heavily on them to execute our trials in a safe, compliant, and timely manner. Although we intend to internalize portions of some of these functions during 2021 and beyond as our organization grows, we expect to continue to rely on these third parties to a significant degree in the future.

If any of our CROs, clinical trial sites, or other third party partners terminates their involvement in one of our clinical trials (or with Diffusion entirely) for any reason, we may not be able to enter into alternative arrangements sufficient to meet our needs, on a timely basis, on commercially reasonable terms, or at all. In addition, if our relationship with clinical trial sites is terminated, we may incur significant additional costs or 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.

We, as well as the CROs and other third-party contractors acting on our behalf, are required to comply with GCP and GLP requirements in all of our clinical trials, which are enforced 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, GLP, or other regulatory requirements, the clinical data generated in our clinical trials may be deemed unreliable and we may be required to perform additional clinical trials to supplement or replace such data before receiving approval of a product candidate from the FDA foreign regulatory authority. Our clinical trials must also generally be conducted with product produced under cGMP regulations. Our and our partners' compliance with these various regulations may be reviewed by regulatory inspections at any time, processes over which we will have very little control or immediate visibility, and a failure to comply with these regulations and policies by us, our CROs, or any of our other third party partners may result in significant delays in our development programs. 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.

In addition, in order to fund or otherwise further development of our current or future product candidates, we may collaborate with other pharmaceutical and biotechnology companies on their development and potential commercialization of those product candidates. We would face significant competition in seeking appropriate partners and whether we reach a definitive agreement for a collaboration will depend on many factors, including, our assessment of a partner's resources and experience, the terms and conditions of the proposed collaboration, the likelihood of approval by the FDA or other regulatory authorities; the potential market for the subject product candidate; uncertainty with respect to our ownership of our intellectual property; and industry and market conditions generally. These types of collaborations are complex and time-consuming to negotiate and document and could ultimately result in lower returns on investment for our stockholders than would have been achieved developing the product candidate without a partner. Further, if we were to breach our obligations under the agreements governing any such future collaboration, 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.

Any failure to successfully enter into and maintain the necessary relationships with CROs and our other current and future third party partners and collaborators could materially and adversely affect our business, financial condition, and results of operations.

General Risks Related to the Development, Regulatory Approval, and Commercialization of TSC and Our Other Product Candidates

Our business, financial condition, or results of operations may also be materially adversely affected by a number of general risks related to the development and regulatory approval of our product candidates that are not specific to our Company, including:

- Our COVID Trial, which we completed in February 2021, was conducted in Bucharest, Romania and we may in the future conduct additional clinical trials for TSC or our other product candidates outside the U.S. In connection with an application for marketing approval, the FDA may determine not to accept data from clinical trials conducted outside of the U.S. if they determine the data presented therefrom cannot be considered valid without further inspection of the clinical trial site, are not applicable to the U.S. population and U.S. medical practice, or as a result of certain other factors. There can be no assurance that the FDA will accept any data we obtain from the COVID Trial or other trials we may conduct outside the U.S. in the future.

- We face a number of risks related to the potential for one or more of our future product candidates to cause undesirable side effects, have other unexpected properties, contain manufacturing defects, or be subject to misuse or abuse. The occurrence of one or more of these events with respect to a product candidate or product could delay or prevent its regulatory approval, limit its commercial potential, result in additional pre- or post-approval regulatory requirements, or subject us to product liability exposure to consumers, health care providers, or others. Product liability claims could be brought in the future even if a product candidate is ultimately approved for commercial sale and manufactured in facilities licensed and regulated by the appropriate governmental authorities, and if product liability claims brought against us in the future were to be successful, we could incur substantial liability if our insurance coverage for those claims proved to be inadequate.

- Our employees, independent contractors, principal investigators, consultants, vendors, CROs, and other third parties we work with in the course of our development activities may engage in misconduct or other improper activities, including noncompliance with regulatory standards and requirements, during the course of their employment or other engagement with us. Any such misconduct or improper activities, whether intentional or negligent, could result in regulatory sanctions or other penalties against the Company, exclusion from federal healthcare programs such as Medicare and Medicaid, the incurrence of substantial defense costs, and serious harm to our reputation.

In addition, although we currently have no marketed products, in the event TSC or any of our other product candidates are approved for marketing and commercial sale by the FDA or any other regulatory authority, our business, financial condition, or results of operations may be materially adversely affected by a number of general risks related to the commercialization of such products that are not specific to our Company, including:

- 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 degree and rate of physician and patient adoption will depend on a number of factors, including the clinical indications for which a product candidate is approved and its effectiveness compared to other therapies, cost and the availability of reimbursement and other coverage from third party payors, our ability to educate patients and healthcare providers regarding a new therapy, and the effectiveness of our sales and marketing efforts. Furthermore, we will face significant competition, often from products sold and marketed by companies with far greater resources than Diffusion, and our failure to effectively compete may prevent us from achieving significant market penetration.

- With respect to any such future products available only by prescription, if we are unable to achieve and maintain coverage and adequate levels of reimbursement from third party payors – including governmental health programs such as Medicare and Medicaid and private insurance companies – and access to such third party payors' drug formularies, the commercial success of those products may be severely hindered. If any such products do not demonstrate attractive efficacy profiles, they may not qualify for coverage and reimbursement and, even if we obtain coverage for a given product, the resulting reimbursement payment rates might not be adequate, may require co-payments that patients find unacceptably high, and may vary from payor to payor, and there is no assurance that coverage and reimbursement levels necessary to achieve commercial success will be obtained.

- Any such future products candidates that we commercialize will be subject to ongoing and continued regulatory review, including rules and regulations of the FDA and similar non-U.S. governmental authorities relating to advertising, marketing and labeling (including restrictions on the promotion of off-label use), potential REMS requirements, routine manufacturing and other review, and required compliance with GLP. If we or a regulatory agency discovers previously unknown problems with any such product, or any facility at or process by which it is manufactured, we may face restrictions on the sale or distribution of such product or on our Company as a whole, including regulatory actions requiring us to modify marketing or sales materials, suspend manufacturing or ongoing trials, initiate a recall or withdraw the product from the market entirely, enter into a consent decree, or submit to other civil or criminal investigations and penalties. 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.

- The biopharmaceutical and pharmaceutical industries are highly regulated and the potential for future legislative reform provides uncertainty and potential threats to our business and our potential future revenue and profitability of any such future products. In the U.S., there have been, and we expect there will continue to be, a number of legislative and regulatory changes to the healthcare system intended to contain or reduce the costs of medical products and medical services including those described under the heading *Part I – Item 1. Business – Certain Other Legislation and Regulations – Current Healthcare Laws and Regulations*. 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. We cannot predict the likelihood, nature, or extent of government regulation that may arise from future legislation or administrative or executive action, whether in the U.S. or other market territories we may pursue.

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.

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, and we face competition from a number of sources, such as pharmaceutical companies, generic drug companies, biotechnology companies and academic and research institutions. Accordingly, our ability to obtain and maintain patent protection in both the U.S. and non-U.S. jurisdictions will be critical to our ability to successfully develop, obtain regulatory approval for, and, in particular, commercialize TSC and our other product candidates. These protections are and will be essential to preserving and protecting our novel inventions, proprietary developments, and trade secrets and to preventing third parties from infringing upon them. In particular, 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 in the U.S. and worldwide.

Our patent portfolio includes patents and patent applications in the U.S. and other major markets covering our technology with varying scope, including issued U.S. patents related to composition of matter, formulation, methods of delivery, and methods of use and the scope of coverage vary from country to country. Although we believe that our intellectual property position is strong and are currently assessing our operations and existing portfolio for additional intellectual property opportunities, we do not have – and may be unable to obtain – patent protection for every aspect of our technology. For aspects of our technology for which we do not have patent coverage, or in countries where we do not have granted patents, we may not have any ability to prevent the unauthorized use of our technologies or technologies substantially similar to ours, and any patents that we may obtain in the future 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.

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. The patent application process, also known as patent prosecution, is expensive and time-consuming, and we 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 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. While we are currently engaged in efforts to obtain additional intellectual property and patent protections for TSC, there is no assurance we will obtain such protections through our applications. Therefore, these and any of our patents and applications may not be prosecuted and enforced in an optimal manner. It is also 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 inadvertent prior public disclosures, proper priority claims, inventorship, claim scope, or patent term adjustments. If our current or future third party development partners are not fully cooperative or disagree with us as to the prosecution, maintenance, or enforcement of any patent rights, those patent rights could be compromised and we might not be able to prevent third parties from making, using and selling competing products. Moreover, our competitors may independently develop equivalent knowledge, methods and know-how. Accordingly, we cannot guarantee that any patents will issue from any of our currently pending patent applications, which could impair our ability to prevent competition from third parties.

Even for aspects of our technology for which we have obtained, or obtain in the future, patent protection, the complexity of legal and factual questions underlying such claims means they 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. 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. 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. Changes in either the patent laws or in the interpretations of patent laws in the U.S. and other countries may diminish the value of our intellectual property.

In addition, patents have a limited lifespan, presenting further challenges in effectively protecting our technologies and associated commercial position. In the U.S., the natural expiration of a patent is generally 20 years after it is filed. Various extensions may be available under a variety of legislative and regulatory avenues but often the life afforded by these extensions and the protections they afford are limited relative to full patent protection. 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. Even if patents covering our products are obtained, once the patent life has expired, we may be open to competition from competitive products. If one of our products requires extended development, testing and/or regulatory review, patents protecting such products might expire before or shortly after such products are commercialized. As a result, our owned and licensed patent portfolio may not provide us with sufficient rights to exclude others from commercializing products similar or identical to ours, which could have a material adverse effect on our business, financial condition and results of operations.

To this point, we have been developing TSC since the founding of Diffusion LLC in the early 2000s and, as a result, portions of our patent portfolio, including certain patents related to TSC's composition of matter, will expire beginning in 2023, which may be prior to the time that we are able to obtain regulatory approval for and, if approved, commercialize TSC. Moreover, the normal life (i.e., with no adjustments or extensions) of our key issued patents related to the composition of matter of TSC extends to 2026, with potential patent term extensions to 2031, and the normal life of our patents related to an oral formulation of TSC extends to 2031, with potential patent term extensions to 2036. While the Company is actively engaged in efforts to obtain additional patent protection covering our product candidates, there is no assurance that we will successfully obtain such patent protection.. As a result, our owned and licensed patent portfolio may not provide us with sufficient rights to exclude others from commercializing products similar or identical to ours. For example, we are aware of other companies that currently use different formulations of TSC, which could adversely affect the Company.

Furthermore, 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. 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 in those countries. 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.

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 U.S. may be less willing to protect trade secret information.

If we are unable to adequately obtain or enforce our patent and other intellectual property rights for any reason, it could materially and adversely affect our business, financial condition, and results of operations. For more information about our intellectual property and our competition, see the information included under the heading, "Part I – Item 1. Business – Products, Product Development, and Our Competition – Our Intellectual Property" and "— Our Competition."

If we become involved in lawsuits to protect or enforce our patents or other intellectual property, or 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, financial condition, or results of operations.

Our ultimate commercial success depends upon our ability to develop, manufacture, market, and sell our product candidates and use our proprietary technologies in the U.S. and non-U.S. markets. In order to do so, it is critical that we prevent third parties from infringing on our intellectual property rights and that we operate our business without infringing on the intellectual property rights of others.

However, numerous U.S. and non-U.S. issued patents and pending patent applications owned by third parties exist in fields relating to TSC and our other product candidates, their potential methods of delivery, potential indications they may be used to treat, and their other features, and, as more patents are issued over time, the risk increases that others may assert that our product candidates, technologies, or methods of delivery or use infringe their patent or other intellectual property rights, or that we discover a third party infringing on our 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, which of these patents may be valid and enforceable, and what inventions or technologies may be claimed by non-public patent applications. Patent applications in the U.S. and many foreign jurisdictions are typically not published until 18 months after their first non-provisional filing and publications in the scientific literature often lag behind actual discoveries, meaning we cannot be certain whether others, including our competitors, have filed patent applications for technology covered by patents or our pending applications and whether any such filing has priority over our own applications or patents.

In the biopharmaceutical and pharmaceutical industries in particular, there is a substantial amount of litigation involving patent and other intellectual property rights. This type of litigation may occur unexpectedly but may also be prompted by specific events, such as a patent application being made public by the USPTO or a non-U.S. governmental authority or under Paragraph IV of the Hatch-Waxman Amendments. For more information regarding the Hatch-Waxman Amendments and Paragraph IV thereunder, see the information included under the heading, "*Part I – Item 1. Business – Government Regulation – The Hatch-Waxman Amendments*."

As of the date of this Annual Report, no litigation asserting infringement claims has been brought against us, nor have we filed such a claim against any third party. However, we cannot assure you that the development or future commercialization of any of our product candidates or other technologies will not result in claims that our activities infringe on the existing or future intellectual property rights of third parties. Furthermore, potential competitors may infringe our intellectual property, including our patents. For example, in the first quarter of 2021, we became aware of a third party affiliated with a former outside consultant of the Company which claims to be in early-stage development of a product candidate that purportedly may operate through a similar mechanism of action to TSC.

We may be required to file infringement claims to stop third-party infringement or unauthorized use or, if a third party claims we are infringing on their rights, respond to such claims. This process can be expensive and time consuming, and could result in a court deciding that a patent of ours is not valid or is unenforceable, that a third party is not required to stop using a technology we believe infringes on our rights, significant costs, or the diversion of management's time. An adverse determination in 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 in a manner sufficient to support our development and commercialization needs or that such product candidate needs to be significantly redesigned, or put our pending patent applications at risk of not issuing, or issuing with limited and potentially inadequate scope. Further, 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, interference, derivation, or other proceedings brought at the USPTO may be necessary to determine the priority or patentability of inventions with respect to our patents or patent applications. Litigation or USPTO proceedings brought by us may fail or may be invoked against us by third parties. Even if we are successful in these proceedings, domestic or foreign litigation or USPTO or foreign patent office proceedings may result in substantial costs and the diversion of management's time. We may not be able to prevent all misappropriation of our proprietary rights, particularly in countries with a legal framework that offers limited intellectual property protections or where the costs of enforcement outweigh the commercial and other benefits of maintaining intellectual property protections.

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, including as a result of public announcements of the results of hearings, motions or other interim proceedings or developments, or public access to related documents. This type of disclosure could put us at a significant competitive disadvantage by disclosing important trade secrets or other proprietary information to our competitors and other third parties.

Any litigation or other challenge related to our intellectual property could materially and adversely affect our business, financial condition, and results of operations.

General Risks Related to Our Intellectual Property

Our business, financial condition, or results of operations may also be materially adversely affected by a number of general risks related to our intellectual property that are not specific to our Company, including:

- As is common in the biopharmaceutical and pharmaceutical industries, some of our employees were formerly employed by companies in the industry, including our competitors or potential competitors, and some of our consultants actively work for other companies in the industry. As a result, although we have in place policies which prohibit the use of third-party confidential information in violation of any obligation to a former employer or otherwise, 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. In addition, if any of our current employees or consultants are engaged by a competitor in the future, it is possible that they may appropriate or otherwise improperly use our proprietary and confidential information. Any of the foregoing events could result in significant costs and the diversion of time and resources.

- 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 as a result of any non-compliance with these requirements. We may also abandon certain intellectual property protections that we would otherwise maintain if we determine such protections are not expected to provide sufficient value relative to the cost of ongoing maintenance.

- Patent laws and other intellectual property protections available in the U.S., E.U., or other jurisdictions are subject to change. These changes may be unpredictable, weaken our overall intellectual property position, increase our costs related to maintenance and enforcement, or otherwise diminish the value of patents in general, thereby impairing our ability to protect our product candidates and maximize our return on investment thereon.

Risks Related to Our Business, Financial Position, Results of Operation, and Organizational Structure

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 forced to delay or curtail our clinical trials and other development activities or be unable to complete the development and commercialization of our product candidates due to a lack of sufficient resources.

Although we expect that our existing cash resources will enable us to fund our operating expenses and capital expenditure requirements through 2023, we expect to continue to spend substantial amounts as we continue to develop TSC and our other product candidates. As a result, we will need to obtain additional financing in the future in order to complete the development of TSC and fund our other development and operational activities.

We cannot be certain that the additional funding we will require will be available on acceptable terms or at all. Investors may demand significant discounts to market prices or that we agree to restrictive covenants or other limitations on our ability to operate our business, and conditions in the capital markets may make equity and debt financing more difficult to obtain or negatively impact our ability to complete a financing transaction at all. 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, discontinue the development or commercialization of one or more of our product candidates, or seek alternative financing opportunities such as collaborations or licensing opportunities. For example, prior to completing the May 2020 Offering and February 2021 Offering, we determined that we did not have adequate resources to fully support the randomized portion of the GBM Trial and commencement of enrollment in the trial was suspended following the run-in portion.

Furthermore, 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 the associated risks and uncertainties. Although we have based this estimate on assumptions that we believe to be reasonable, they may prove to be wrong, we could utilize our available capital resources sooner than we currently expect, and actual results could vary greatly from our expectations expressed in this Annual Report as a result. The magnitude and timing of our future funding requirements, both near and long-term, will depend on many factors, including, but not limited to:

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

We currently generate no revenue from the sale of products, have incurred significant losses since our inception, have a history of net losses and negative cash flow from operations, expect to incur losses for the foreseeable future, and may never become profitable. In addition, 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. As a result, any investment in our common stock is speculative and risky.

We are a clinical stage biotechnology company and, as a result, we have a limited operating history from which to assess how we will respond to competitive, economic, or other challenges to our business, and 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, including the development of TSC and our other product candidates. To date, we have not yet obtained regulatory approvals for any of our product candidates and, accordingly, have not generated any revenues from the sale of products. We expect to continue to incur losses and negative cash flow for the foreseeable future. Furthermore, our future 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 delays in our product development programs including as a result of regulatory review, increased expenditures related to manufacturing or the enforcement of intellectual property rights, other litigation costs, changes in accounting policies, or other unanticipated events.

Our ability to generate sufficient revenues from TSC or any of our other product candidates, if approved, will depend on numerous factors described throughout this Annual Report. Even if we are able to successfully develop and receive regulatory approval for TSC or any of our other product candidates, we do not know if or when any such product will achieve commercial success or generate revenue for us, and we will incur significant costs associated with the commercialization that will need to be offset by revenue before achieving a profit. We may also in the future enter into collaboration agreements and license agreements with other companies that include milestone expenditures and payments, in which case our ability to generate revenue or achieve profitability may be dependent on the achievement of those milestones. Even if we achieve profitability in the future, we may not be able to sustain profitability in subsequent periods, and our prior losses and expected future losses have had and will continue to have an adverse effect on our stockholders' equity. Furthermore, due to the uncertainty of the drug development process, we are often unable to predict the timing or amount of increased expenses, or when we will be able to achieve or maintain profitability, if at all.

We will need to further increase the size and complexity of our organization in the future including, if TSC or any of our other product candidates are approved for commercial sale, establishing sales and marketing capabilities. We may experience difficulties in executing our growth strategy or managing any growth that we do experience if we are unable to recruit and retain talented individuals in key positions.

Our ability to succeed in the highly competitive pharmaceuticals industry depends upon our ability to attract and retain highly qualified personnel. As of the date of this Annual Report, we have 14 full-time employees and no part-time employees. Particularly given our near-term plans for the TSC development program and our compliance requirements with the FDA, SEC, and other regulatory bodies, we believe that our current staffing levels are inadequate to support our future needs. We anticipate adding additional personnel to our team throughout the organization during 2022 in an effort to support the development of TSC, grow our business more generally, and optimize the size of our organization. In addition, assuming success in our ongoing and planned clinical trials, we expect to further supplement and grow our scientific, clinical, regulatory, financial, and other human resources to support our planned research, development, and commercialization plans for TSC and our other product candidates.

Our ability to effectively manage our anticipated growth will depend on multiple factors, including, among others, our ability to:

- effectively retain current talent and effectively recruit sufficient numbers of new talented employees;
- 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;
- establish and maintain relationships with development and commercialization partners;
- manage our development and commercialization efforts effectively and in a cost-effective manner; and
- continue to improve our operational, clinical, financial, management and regulatory compliance controls and reporting systems and procedures.

We are highly dependent on our management and scientific personnel, including our executive officers, certain other key employees and consultants, and the members of our Board. The loss of the services of any of these individuals could impede, delay, or prevent completion of our ongoing and planned clinical trials, regulatory approval, or commercialization of TSC or any of our other product candidates. 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. All of our employees, including our executive officers with whom we have employment agreements, are employed on an at-will basis and their employment can be terminated by us or them at any time. As part of our efforts to retain our valuable employees, we, among other things, provide a generous salary and benefits package, as described in more detail under the heading, "*Part I — Item 1. Business – Our People and Human Capital Resources – Employees*."

Nevertheless, we may be unable to attract or retain qualified management and other key personnel in the future due to the intense competition among biotechnology, pharmaceutical, and other businesses. There may be a limited number of persons with the requisite skills to serve in these positions, and we cannot assure you that we will be able to identify or employ qualified personnel for any such position on acceptable terms, if at all, and the high levels of competition within the industry may mean that we will 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. Furthermore, as we currently have no marketed products, we currently have no sales or marketing personnel or capabilities. To commercialize TSC or any of our other product candidates, if approved, we will need to build our marketing, sales, distribution, and other related capabilities or arrange with third parties to perform these services, and we may not be successful in doing so.

In addition, we have historically utilized the services of certain outside independent contractors to perform a number of critical functions for our company, including with respect to clinical development, regulatory matters, accounting, and human resources, a practice we expect to continue and may choose to expand in the future. We rely on these independent contractors and effectively managing our relationships with them is and will remain a priority. However, there can be no assurance that we will be able to manage these relationships effectively, that such contractors will be able or choose to continue working with us in the future, or that we will be able to find additional or replacement services if and as needed, on economically reasonable terms or at all.

If we are not able to effectively manage our growth and expand our organization through a combination of effectively retaining our existing employees and third-party contractors and successfully recruiting new employees and contractors, we may be unable to effectively execute on our product development and other strategic plans, which may adversely affect our business, financial condition, or results of operations.

If we decide to in-license or acquire one or more additional product candidates or otherwise enter into a strategic transaction, it could impact our liquidity, increase our expenses, and present significant distractions to our management team.

We currently only have one product candidate under active development, TSC. We may in the future implement a strategy to in-license or acquire one or more additional product candidates to supplement our pipeline. We may also consider a variety of other strategic transactions, including spin-offs, partnerships, joint ventures, restructurings, divestitures, business combinations, and minority investments. Any such transaction would expose us to a number of risks and uncertainties, including the potential incurrence of recurring, non-recurring (including unknown liabilities), or other charges (including amortization expenses, write-downs, or other impairment charges), increase of short- and long-term expenditures, or dilution to our stockholders, as well as posing significant integration, implementation, or retention challenges and diverting our management team's focus on other priorities, including the TSC development program. Any of the foregoing could have a material adverse effect on our business, financial condition, or results of operation. which could adversely affect our operations and financial results. There can be no assurance that we will undertake such a transaction or, if we do, that we will successfully complete the transaction or that the transaction will be additive to our business, financial condition, or results of operations.

Our ability to utilize our NOL carryforwards and other deferred tax assets may be limited as a result of past and future issuances of our common stock.

As of December 31, 2021, we had $23.4 million in federal and state NOL carryforwards available to reduce future taxable income, if any, for income tax purposes. If not utilized, the NOL carryforwards will begin expiring during the year ending December 31, 2034. Under Section 382 of the Tax Code, if a corporation undergoes an "ownership change," generally defined as a greater than 50% change, measured by value, in its equity ownership over a three-year period, the corporation's ability to use its pre-ownership change NOL carryforwards and other pre-ownership change tax attributes – such as research tax credits – to offset its post-ownership change income may be limited. In the event we issue additional shares of common stock to fund our future development efforts and those issuances result in additional ownership changes for purposes of Section 382 of the Tax Code, as we did in the May 2020 Offering and the February 2021 Offering, our NOL carryforwards could be further reduced.

General Risks Related to Our Business, Financial Condition, Results of Operations, and Organizational Structure

Our business, financial condition, or results of operations may also be materially adversely affected by a number of general risks related thereto and to our organizational structure that are not specific to our Company, including:

- 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. Furthermore, our disclosure controls and procedures are subject to inherent limitations, human error, and other systematic breakdowns, and therefore may not prevent or detect all errors or acts of fraud. As a result, stockholders could lose confidence in our financial and other public reporting, which could harm our business, financial condition, or results of operations.

- As our Company, the industry in which we operate, and the world-at-large become increasingly virtual, our acquisition and implementation of additional information technology solutions and our compliance with global privacy and data security requirements could result in additional costs and liabilities or inhibit our ability to collect and process data globally. Furthermore, any failure to comply with applicable requirements or best practices – as well as other events outside of our control – could result in a security breach or other disruption to our information technology systems, limit our capacity to effectively monitor and control our operations, compromise our or third parties' confidential information, or otherwise adversely affect our business, financial condition, or results of operations.

- We incur significant costs as a result of our public company status and devote substantial management time to operating as a public company, including complying with the applicable requirements of the Securities Act, the Exchange Act, the Dodd-Frank Act, SOX, and the rules and regulations of Nasdaq. If, in the future, we are required to include in our annual report an attestation of our independent registered public accounting firm regarding internal control over financial reporting, the amount of these compliance costs would increase significantly.

- Although we have in place business continuity and disaster recovery plans, our business, financial condition, or results of operations could be negatively affected by volatility, disruptions, or other uncertainty caused by market fluctuations, economic downturns or unfavorable global economic conditions, pandemics, natural disasters or other catastrophic events, events of war, terrorism, or other man-made problems, or other geopolitical events outside of our control, including the COVID-19 pandemic and Brexit.

- If we fail to comply with applicable laws and regulations, including the healthcare laws and regulations described under the heading, *Part I – Item 1. Business – Certain Other Legislation and Regulations – Current Healthcare Laws and Regulations* and applicable environmental, health, and safety laws and regulations, we could become subject to fines, penalties, or other consequences.

Risks Related to Ownership of Our Common Stock

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 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 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 regain and continue to meet the Bid Price Rule and Nasdaq's other listing requirements.

As previously disclosed, on May 6, 2021, we received a written notice from the Staff indicating that the Company was not in compliance with the Bid Price Rule because the bid price for the Company's common stock had closed below $1.00 per share for the previous 30 consecutive business days. On November 3, 2021, after failing to regain compliance with the Bid Price Rule within 180 days of receipt of the first notice, we received an additional notice from the Staff providing that, although the Company had not regained compliance with the Bid Price Rule by the previously stated deadline, in accordance with Nasdaq Listing Rule 5810(c)(3)(A), the Company would be granted an additional 180 calendar days, or until May 2, 2022, to regain compliance with the Bid Price Rule.

To regain compliance with the Bid Price Rule, the bid price for our common stock must close at $1.00 per share or more for a minimum of 10 consecutive business days. NASDAQ's written notice has no effect on the listing or trading of our common stock at this time, and we are currently evaluating our alternatives to resolve this listing deficiency. We have filed with the SEC a proxy statement relating to the Special Meeting, to be held on April 14, 2022, at which our stockholders will vote on a proposal to approve an amendment to our Certificate of Incorporation to effect the Reverse Stock Split, with the final decision of whether to proceed with the Reverse Stock Split, the effective time of the Reverse Stock Split, and the exact ratio of the Reverse Stock Split to be determined by the Board, in its discretion, at any time prior to December 31, 2022. However, there can be no assurance that the Reverse Stock Split will be approved at the Special Meeting or, if approved, will result in a sustained higher stock price, if effected, that will allow us to regain compliance with the Bid Price Rule and meet the NASDAQ stock price listing requirements, and there is no guarantee we will continue to satisfy the other 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 for us to raise capital and for our stockholders 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.

Our stock price is volatile and any investment in our securities may suffer a decline in value. In addition, this volatility may subject our business to additional risks, such as an increased risk of securities litigation.

During the year ended December 31, 2021, the closing market price for our common stock as reported by Nasdaq varied between a high of $1.70 on February 16, 2021 and December 31, 2021 and a low of $0.31 on December 29-31, 2021. As a result of fluctuations in the price of our common stock, you may be unable to sell shares or our common stock at or above the price you paid for them, even if your holding period is relatively short. The market price of our common stock is likely to continue to be volatile and subject to significant price and volume fluctuations in response to market, industry and other factors, including the degree of analyst coverage of our stock, their valuations and recommendations, and whether any such analysts publish inaccurate or unfavorable research about our business. If the results of our business do not meet these analysts' forecasts, the expectations of investors or the financial guidance we provide to investors in any period, the market price of our common stock could decline. Furthermore, despite this volatility, due to the fact that we have never declared or paid cash dividends on our common stock and do not currently anticipate declaring or paying any cash dividends in the foreseeable future, we expect that only appreciation of the price of our common stock, if any, will provide a return to our stockholders for the foreseeable future.

Historically, the stock markets in general, and the markets for biotechnology stocks in particular, have experienced significant volatility that has at times been unrelated to the financial condition or results of operations of particular companies. These broad market fluctuations may adversely affect the trading price of our common stock and, consequently, adversely affect the price at which you are able to sell any shares of our common stock that you own. In the past, following periods of volatility in the market or significant price declines in individual securities or the market as a whole, securities class-action litigation has often been instituted against companies. Such litigation, if instituted against us, could result in substantial costs and diversion of management's attention and resources, which could materially and adversely affect our business, financial condition, results of operations and growth prospects.

We have funded our operations to date through the issuance of securities, including common stock, warrants to purchase common stock, convertible preferred stock, and convertible debt securities, and we expect that in the future we will need to raise additional capital through similar means to fund our continued development efforts for TSC and our other liquidity needs. Assuming funding is available on acceptable terms, any future issuance of common stock or securities convertible for or exchangeable into common stock will result in dilution to our existing stockholders and could depress the market price of our common stock. Furthermore, the terms of future financing transactions may contain provisions that restrict our operations or require us to relinquish certain rights to our product candidates or other technologies.

Although we believe we have sufficient cash resources to fund our other operating expenses and capital expenditure requirements through 2023, we will in the future need to raise additional funds to continue our operations, fund additional clinical trials evaluating TSC and our other product candidates, and, if approved, commercializing TSC. We plan to continue to finance our operations with a combination of equity issuances, debt arrangements, and, potentially, licensing, or other partnering relationships. In addition, our Board may determine at any time to raise additional capital if it believes the terms are in the best interests of our stockholders.

Accordingly, new issuances of a substantial number of shares of our common stock could occur at any time. For example, in February 2021, we issued approximately 33.7 million shares of our common stock in connection with the completion of the February 2021 Offering. Any issuance or sale of shares, or the perception in the market of an intent to issue or sell shares in the near-term, by the Company or holders of a large number of shares could reduce the market price of our common stock. We also cannot assure you that any such sale of common stock or other securities will be at a price per share that is equal to or greater than the price per share paid by you for our common stock. Furthermore, a depressed stock price could limit our ability to raise necessary capital through the sale of additional equity securities on terms that are acceptable.

We may also seek additional capital through other methods, either alone or in combination with the issuance of additional securities, including debt financings, receivables or royalty financings, strategic partnerships and alliances, and licensing arrangements, any of which could be coupled with an equity component, such as warrants to purchase stock. The incurrence of indebtedness could result in increased fixed payment obligations, liens and other security interests being placed on certain of our assets, and certain restrictive covenants being imposed on the operation of our business, such as limitations on our ability to incur additional debt or acquire intellectual property rights. We may also in the future raise additional funds through strategic partnerships, alliances, and licensing arrangements with third parties, any of which could require us to relinquish valuable rights to TSC or our other product candidates. The restrictions imposed by any of these arrangements could materially decrease any potential returns on our investment in TSC or our other product candidates, or otherwise materially and adversely affect our business, financial condition, or results of operations.

Our organizational documents impose certain anti-takeover provisions and make the Delaware Chancery Court the exclusive forum for certain stockholder actions, which could depress the trading price of our common stock.

Our certificate of incorporation, as amended, and our Bylaws contain provisions that may make the acquisition of our company, a proxy contest, or the nomination of a director candidate by a stockholder more difficult than such actions would be in the absence of such provisions, including that:

- only our Board has the right to fill a vacancy on the Board created by an expansion or by the resignation, death, or removal of a director, which prevents stockholders from being able to fill vacancies on our Board;
- only our Chairman of the Board, our Chief Executive Officer, or a majority of our directors are authorized to call a special meeting of stockholders;
- we may issue undesignated preferred stock, the terms of which may be established and shares of which may be issued without stockholder approval (notwithstanding any requirements imposed by the SEC or any exchange on which our common stock may now or in the future trade), and which may include rights superior to the rights of the holders of common stock;

- our Board is expressly authorized to amend, restate, or repeal our Bylaws; and
- advance notice is required with respect to any nominations for election to our Board or for proposing matters that can be acted upon by stockholders at any meeting of stockholders.

In addition our Bylaws provide that, unless we consent in writing to the selection of an alternative forum, the Court of Chancery of the State of Delaware is the sole and exclusive forum for certain actions, including derivative actions brought on the Company's behalf, stockholder actions claiming breaches of a fiduciary duty owed by any of our directors or officers, and claims arising under our organizational documents, in each case, subject to said Court of Chancery having personal jurisdiction over the indispensable parties named as defendants therein. Although this provision would not apply to any stockholder claims under the Exchange Act, there is uncertainty regarding whether a court would enforce such a forum selection provision as written to stockholder claims under the Securities Act. Nevertheless, this forum selection provision may limit our stockholders' ability to obtain a favorable judicial forum for disputes with us or our directors, officers, employees, or agents, which may discourage lawsuits against us and such persons.

The limitations on certain stockholder rights imposed by these provisions could also depress the trading price of our common stock.

ITEM 1B. UNRESOLVED STAFF COMMENTS

None.

ITEM 2. PROPERTIES

On November 8, 2021, the Company entered into a Deed of Lease Termination Agreement with the Carlton Landlord providing for the early termination of the Carlton Lease related to the Company's prior corporate headquarters. The Carlton Lease was previously scheduled to expire on April 30, 2022. In connection with the termination, the Company made a one-time payment to the Carlton Landlord of approximately $14,000, net of a security deposit subsequently returned in accordance with the Carlton Lease. In lieu of the fixed office and laboratory space previously available to us under the Carlton Lease, the Company has entered into short term agreements to utilize membership-based co-working space in both Charlottesville, Virginia and Philadelphia, Pennsylvania.

ITEM 3. LEGAL PROCEEDINGS

The information in *Note 6, Commitments and Contingencies — Legal Proceedings* to our consolidated financial statements set forth in, *Part II — Item 8 — Financial Statements* of this Annual Report is incorporated herein by reference.

In addition, 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.

ITEM 4. MINE SAFETY DISCLOSURES

None.

PART II

ITEM 5. MARKET FOR REGISTRANT'S COMMON EQUITY, RELATED STOCKHOLDER MATTERS AND ISSUER PURCHASES OF EQUITY SECURITIES

Market Information

Our common stock trades publicly on the Nasdaq Capital Market under the symbol "DFFN."

Holders

As of March 15, 2022, there were 343 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.

Securities Authorized for Issuance Under Equity Compensation Plans

The information set forth in, *Part III — Item 12 (Security Ownership of Certain Beneficial Owners and Management and Related Stockholder Matters)* of this Annual Report is incorporated herein by reference to the extent required by Item 201(d) of Regulation S-K.

Recent Unregistered Sales of Equity Securities and Use of Proceeds

None

Purchases of Equity Securities by the Issuer and Affiliated Purchasers

None.

ITEM 6. SELECTED FINANCIAL DATA

The information required by Item 6 of Form 10-K has been omitted from this Annual Report pursuant to the amendments to Regulation S-K adopted by the SEC on November 19, 2020.

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

Introduction

This discussion and analysis contains information related to historical and prospective events intended to enable you to assess our financial condition and results of operations. The information contained in this discussion and analysis should be read in conjunction with our consolidated financial statements and the related notes contained elsewhere in this Annual Report, as well as the risks and uncertainties discussed under the heading, "*Part 1A — Risk Factors.*"

Diffusion Pharmaceuticals: Enhancing Oxygen, Fueling Life

We are a biopharmaceutical company developing novel therapies that enhance the body's ability to deliver oxygen to the areas where it is needed most. Our lead product candidate, TSC, is being developed to enhance the diffusion of oxygen to tissues with low oxygen levels, also known as hypoxia, a serious complication of many of medicine's most intractable and difficult-to-treat conditions.

Highlights from Fourth Quarter of 2021

- *Announced Lead Development Program* – In November 2021, we announced our intent to develop TSC as an adjunct to standard of care therapy for hypoxic solid tumors.

- *Initiated Final Two Oxygenation Trials* – On November 22, 2021, we announced dosing of the first participants in the Altitude Trial and, on December 16, 2021, we announced dosing of the first patients in the ILD-DLCO Trial. We currently expect to complete dosing in the Altitude Trial in the first quarter of 2022 and to complete dosing in the ILD-DLCO Trial in the second quarter of 2022.

- *Enhanced Intellectual Property Portfolio* – On November 30, 2021, the USPTO granted to the Company United States Patent No. 11,185,523, "Use of Bipolar Trans Carotenoids With Chemotherapy and Radiotherapy for Treatment of Cancer." This patent includes new claims related to methods of treating cancerous tumors by administering TSC in combination with radiation therapy and chemotherapy. This new patent extends the normal life of our cancer-related intellectual property claims into 2037.

- *Implemented Cost-Saving Facility Changes* – In November 2021, we terminated the Carlton Lease for our prior corporate headquarters, furthering our shift to a remote-work culture. During 2021, we also entered into short-term agreements to utilize membership-based co-working space in both Charlottesville, Virginia and Philadelphia, Pennsylvania, resulting in cost savings.

Our Strategic Priorities for 2022

In 2022, we plan to continue and further our focus on the development of TSC for the treatment of hypoxia and as a platform to enhance standard-of-care treatment for conditions complicated by hypoxia with a particular near-term focus on hypoxic solid tumors.

As of March 15, 2022, TSC has been administered to more than 220 subjects across 11 clinical trials. Data from these clinical trials support our understanding of the safety, tolerability, pharmacokinetics and pharmacodynamic effects of TSC. In addition, post hoc analyses of two prior studies involving patients with PAD with claudication and unresected GBM tumors have provided preliminary evidence of TSC's potential. However, the data available from these studies and the post hoc analyses of their outcomes are limited in several meaningful ways. For example, neither study was powered to formally demonstrate efficacy at a statistically significant level, there was no evaluation of whether TSC increased oxygenation in the target tissues in either study, and, in the GBM Trial, no dose exploration was conducted.

During 2021, to address these identified gaps in our TSC knowledge base, further inform our identification of potential indications appropriate for TSC, and guide the future of our TSC development program, we designed and executed on our Oxygenation Trials. The Oxygenation Trials are a series of three short-term, clinical studies designed to provide clinical evidence of the relationship between TSC dose and the effects on oxygenation, each specifically tailored to evaluate the effects of TSC on a different component of the oxygen delivery pathway. We completed the first of these studies, the TCOM Trial, in March 2021. The first participants and patients in the remaining two Oxygenation Trials, the Altitude Trial and the ILD-DLCO Trial, were dosed in November 2021 and December 2021, respectively. We currently expect to complete dosing in the Altitude Trial in the second quarter of 2022 and to complete dosing in the ILD-DLCO Trials in the middle of 2022 and, in each case, to report top-line results within two months of study completion.

In November 2021, based on the available preclinical and clinical data and the significant unmet medical need, we announced our intention to focus near-term efforts on developing TSC as an adjunct to standard of care therapy for hypoxic solid tumors. Through the combination of our past experiences, new knowledge gained from our Oxygenation Trials and COVID Trial regarding TSC's effects on oxygenation, dose response characteristics, pharmacokinetics, and pharmacodynamics, and further analyses and discussions of all available data with our Scientific Advisory Board and other external advisors, we believe we now have the necessary information to design the Hypoxic Solid Tumor Program to be more efficient and increase our likelihood of success compared to the Company's past efforts to develop TSC as a cancer treatment, which were terminated in 2019 due to financial constraints.

As part of the ongoing design of our Planned Phase 2 Hypoxic Tumor Trial – the first trial in our Hypoxic Solid Tumor Program which we currently expect to commence in the second half of 2022, subject to FDA feedback and the availability of clinical drug supply – we are currently drafting a trial protocol which we intend to file with the FDA. In parallel, we will continue our work to optimize the TSC manufacturing process and support the continued availability of high-quality drug product and undertake preclinical studies and other opportunities to continue developing data designed to demonstrate TSC's potential uses in a broad spectrum of non-cancer indications.

Financial Summary

As of December 31, 2021, we had a cash and cash equivalents balance of $37.3 million. We have incurred operating losses since inception, have not generated any product sales revenue, and have not achieved profitable operations. We incurred net losses of $24.1 million and $14.2 million for the years ended December 31, 2021 and 2020, respectively. To date, we have funded our operations and short-term liquidity needs primarily through the issuance and sale of common stock, warrants to purchase common stock, convertible debt, and convertible preferred stock. We expect to continue funding our operations through similar means for the foreseeable future, assuming the availability of additional capital, though we may enter into strategic partnerships or other alternative transactions in order to fund our ongoing capital requirements.

Our accumulated deficit as of December 31, 2021, was $130.0 million and we expect to continue to incur substantial losses in future periods for the foreseeable future. We also anticipate that our operating expenses will increase substantially as we continue to advance the development of TSC, including any costs related to:

- our ongoing and planned clinical trials, including the ongoing Oxygenation Trials and our Planned Phase 2 Hypoxic Solid Tumor Trial;
- any additional studies we may undertake to evaluate TSC, including other preclinical and clinical studies to support the filing of any NDA with the FDA;
- near-term investments intended to improve the quality and robustness of our supplier relationships and overall supply chain;

- other research, development, and manufacturing activities designed to develop and optimize formulation, manufacturing processes, dosage, dose forms, and other characteristics prior to regulatory approval;
- the maintenance, expansion, and protection our global intellectual property portfolio;
- the hiring of additional clinical, manufacturing, scientific, sales, or other personnel;
- research and development related to any other product candidates we may acquire or in-license in the future; and
- investments in operational, financial, and management information systems.

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 cash and cash equivalents as of December 31, 2021 will enable us to fund our operating expenses and capital expenditure requirements through 2023.

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

R&D expenses include, but are not limited to, third-party CRO arrangements and employee-related expenses, including salaries, benefits, stock-based compensation, and travel expense reimbursement. R&D 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 studies. As we advance our product candidates, we expect the amount of R&D costs will continue to increase for the foreseeable future. R&D costs are charged to expense as incurred.

Intangible Asset Impairment Charge

In the third quarter of 2021, the Company made a determination to no longer dedicate resources to the Company's DFN-529 intangible asset and any future development efforts were abandoned. In connection with this decision, the Company concluded that DFN-529 was impaired in its entirety.

General and Administrative Expense

G&A expenses consist principally of salaries and related costs for executive and other personnel, including stock-based compensation, other employee benefit costs, expenses associated with investment bank and other financial advisory services, and travel expenses. Other G&A expenses include, facility-related costs, communication expenses and professional fees for legal, patent prosecution and maintenance, consulting, accounting, and other professional services.

Interest Income

Interest income consists of interest earned from our cash and cash equivalents.

Income Tax Benefit

The Company recorded an income tax benefit of $0.4 million during the year ended December 31, 2021. The income tax benefit was due to the tax effect of the reduction in the deferred tax liability associated with the basis difference from the IPR&D indefinite lived intangible asset. The Company maintains a full valuation allowance against its deferred tax assets due to the Company's history of losses as of December 31, 2021.

Our NOLs and tax credit carryforwards are subject to review and possible adjustment by the Internal Revenue Service and state tax authorities. NOL and tax credit carryforwards may become subject to an annual limitation in the event of a greater than 50.0% cumulative change in the ownership interest of significant stockholders over a three year period, as defined under Sections 382 and 383 of the Internal Revenue Code as well as similar state provisions. The amount of the annual limitation is determined based on the Company's value immediately prior to the ownership change, and subsequent ownership changes may further affect the limitation in future years. We have not yet performed an analysis to determine whether or not ownership changes that have occurred in the year ended December 31, 2020 or during the year ended December 31, 2021 give rise to any further limitations.

Critical Accounting Policies and Estimates

Certain of our critical accounting policies require estimates that involve 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 accounting policies described below are among the most critical to aid in fully understanding and evaluating our financial statements, as they require estimates which involve our most subjective or complex judgments.

Intangible Assets

Our sole intangible asset as of December 31, 2020 consisted of DFN-529, which was acquired in 2016 pursuant to our merger with RestorGenex Corporation and was accounted for as an IPR&D intangible asset. The fair value of the IPR&D asset was determined as of the acquisition date using the cost approach, often referred to as current replacement cost, which establishes a value based on the cost of reproducing or replacing the asset. 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 had only completed limited preclinical and clinical trials and the timeline to commercial viability, if the FDA approval process were to be successful, was uncertain, would take a number of years, and the costs would have been significant. In the third quarter of 2021, we made a determination to no longer dedicate resources to our DFN-529 intangible asset and any future development efforts were abandoned. In connection with this decision, we concluded that DFN-529 was impaired in its entirety.

Results of Operations for Year Ended December 31, 2021 Compared to Year Ended December 31, 2020

The following table summarizes our results of operations for the years ended December 31, 2021 and 2020:

	Year ended December 31,		
	2021	2020	Change
Operating expenses:			
Research and development	$ 8,499,414	$ 9,427,667	$ (928,253)
Intangible asset impairment charge	8,639,000	—	$ 8,639,000
General and administrative	7,445,277	6,444,109	1,001,168
Depreciation	93,416	103,168	(9,752)
Loss from operations	(24,677,107)	(15,974,944)	8,702,163
Interest income	137,487	114,257	23,230
Loss from operations before income taxes	(24,539,620)	(15,860,687)	(8,678,933)
Income tax benefit (expense)	443,893	1,675,381	(1,231,488)
Net loss	$ (24,095,727)	$ (14,185,306)	$ (7,447,445)

Research and development expenses were $8.5 million during the year ended December 31, 2021 compared to $9.4 million during the year ended December 31, 2020, a decrease of 10%. This decrease was due to lower project spending due to the completion and/or wind-down of our clinical studies evaluating TSC in Covid-19, GBM, and stroke.

In the third quarter of 2021, the Company made a determination to no longer dedicate resources to the Company's DFN-529 intangible asset and any future development efforts were abandoned. As a result, we recognized a nonrecurring $8.6 million non-cash impairment charge related to the write down of our DFN-529 IPR&D asset.

General and administrative expenses were $7.4 million during the year ended December 31, 2021 compared to $6.4 million during the year ended December 31, 2020, an increase of 16%. The increase was primarily due to increased headcount resulting in higher compensation expense and other costs associated with the hiring of new employees as well as an increase in expense related to consulting services.

For the year ended December 31, 2021, we recognized an income tax benefit of $0.4 million due to the tax effect of the reduction in the deferred tax liability associated with the basis differences from the DFN-529 IPR&D intangible asset that was written down in the third quarter of 2021. For the year ended December 31, 2020, we recognized an income tax benefit of $1.7 million to reflect the utilization of indefinite deferred tax liabilities as a source of income against indefinite lived portions of our deferred tax assets. Prior to 2021, we recognized the full income tax benefit 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.

Liquidity and Capital Resources

Working Capital

The following table summarizes our working capital as of December 31, 2021 and 2020:

	December 31,	
	2021	**2020**
Cash and cash equivalents	$ 37,313,558	$ 18,515,595
Prepaid expenses, deposits and other assets	510,015	260,825
Total current liabilities	2,927,684	2,435,783
Working capital	$ 34,895,889	$ 16,340,637

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 TSC and our other product candidates through 2023.

Cash Flows

The following table sets forth our cash flows for the years ended December 31, 2021 and 2020:

	December 31,	
Net cash (used in) provided by:	**2021**	**2020**
Operating activities	$ (14,501,789)	$ (13,552,629)
Investing activities	4,000	—
Financing activities	33,295,752	17,890,875
Net increase in cash and cash equivalents	$ 18,797,963	$ 4,338,246

Operating Activities

For the year ended December 31, 2021, net cash used in operating activities increased $0.9 million, or 7% compared to the year ended December 31, 2020.

Net cash used in operating activities of $14.5 million during the year ended December 31, 2021 was primarily attributable to our net loss of $24.1 million and a $0.4 million change in deferred income taxes. These amounts were partially offset by a $8.6 million non cash impairment charge in connection with the write down of our DFN-529 IPR&D asset, our net change in operating assets and liabilities of $0.4 million, and non-cash charges comprised of $0.9 million of stock-based compensation expense, the loss on the disposal of property and equipment of $0.1 million and depreciation expense of $0.1 million.

Net cash used in operating activities of $13.6 million during the year ended December 31, 2020 was primarily attributable to our net loss of $14.2 million and a $1.7 million change in deferred income taxes. This amount was offset by our net change in operating assets and liabilities of $1.5 million, and non-cash charges comprised of $0.7 million of stock-based compensation expense and depreciation expense of $0.1 million.

Investing Activities

During the year ended December 31, 2021, we received $4,000 from the sale of property and equipment. For the year ended December 31, 2020, we had no cash flows from investing activities.

Financing Activities

For the year ended December 31, 2021, net cash provided by financing activities increased $15.4 million, or 86% compared to the year ended December 31, 2020.

Net cash provided by financing activities of $33.3 million during the year ended December 31, 2021 was attributable to net proceeds of $31.1 million received from the sale of our common stock in connection with the February 2021 Offering and $2.2 million in proceeds received from the exercise of previously issued common stock warrants.

Net cash provided by financing activities of $17.9 million during the year ended December 31, 2020 was primarily attributable to the $10.8 million in proceeds (net of underwriting discounts and commissions payable by us) received in connection with the May 2020 Offering and $8.0 million in proceeds received in connection with the exercise of common stock warrants stock during the year. These cash inflows were offset in part by the payment of $1.0 million in additional financing costs.

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 TSC. Our operations have consumed substantial amounts of cash since inception and we expect to continue to spend substantial amounts of cash to advance the clinical development of TSC and any other product candidates we may in-license or acquire in the future. As of the date of this Annual Report, most of our cash resources for clinical development are dedicated to our ongoing and planned clinical trials. While we believe we have adequate cash resources to continue operations through 2023, we anticipate that we will need additional funding in order to complete development of TSC which, if available, could be obtained through additional capital raising transactions, entry into strategic partnerships or collaborations, or alternative financing arrangements.

As of December 31, 2021, we did not have any credit facilities in place under which we could borrow funds or any other sources of committed capital. In the future, we may seek to raise additional funds through various sources. However, 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 TSC or our product candidates, or we may need to obtain funds through collaborations or otherwise on terms 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 adequate additional capital as and when required in the future, we could be forced to cease development activities and terminate our operations, and you could experience a complete loss of your investment.

To the extent that we raise additional capital in the future through the sale of our common stock or securities convertible or exchangeable for common stock such as common stock warrants, convertible preferred stock, or convertible debt instruments, the interests of our current stockholders may be diluted or otherwise impacted. 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.

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

The information in *Note 3, Basis of Presentation and Summary of Significant Accounting Policies* to our consolidated financial statements set forth in, *"Part II — Item 8 — Financial Statements*" of this Annual Report is incorporated herein by reference.

ITEM 7A. QUANTITATIVE AND QUALITATIVE DISCLOSURE ABOUT MARKET RISK

As a "smaller reporting company" (as such term is defined in Rule 12b-2 of the Exchange Act), we are not required to provide the information described in Item 305 of Regulation S-K and, accordingly, the information required by Item 6 of Form 10-K has been omitted from this Annual Report.

ITEM 8. FINANCIAL STATEMENTS AND SUPPLEMENTARY DATA

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, 2021 and 2020, the related consolidated statements of operations, changes in 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, 2021 and 2020, and the results of its operations and its cash flows for each of the years then ended, in conformity with U.S. generally accepted accounting principles.

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.

Critical Audit Matters

Critical audit matters are matters arising from the current period audit of the consolidated financial statements that were communicated or required to be communicated to the audit committee and that: (1) relate to accounts or disclosures that are material to the consolidated financial statements and (2) involved our especially challenging, subjective, or complex judgments. We determined that there are no critical audit matters.

/s/ KPMG LLP

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

McLean, Virginia
March 18, 2022

DIFFUSION PHARMACEUTICALS INC.

CONSOLIDATED BALANCE SHEETS

	December 31, 2021	December 31, 2020
Assets		
Current assets:		
Cash and cash equivalents	$ 37,313,558	$ 18,515,595
Prepaid expenses, deposits and other current assets	510,015	260,825
Total current assets	37,823,573	18,776,420
Property and equipment, net	—	149,198
Intangible asset	—	8,639,000
Right of use asset	—	149,162
Other assets	15,578	15,771
Total assets	$ 37,839,151	$ 27,729,551
Liabilities and Stockholders' Equity		
Current liabilities:		
Accounts payable	$ 947,495	$ 545,844
Accrued expenses and other current liabilities	1,980,189	1,776,470
Current operating lease liability	—	113,469
Total current liabilities	2,927,684	2,435,783
Deferred income taxes	—	443,893
Noncurrent operating lease liability	—	35,693
Total liabilities	2,927,684	2,915,369
Commitments and Contingencies (Note 5)		
Stockholders' Equity:		
Common stock, $0.001 par value: 1,000,000,000 shares authorized; 101,914,280 and 64,015,441 shares issued and outstanding at December 31, 2021 and 2020, respectively	101,914	64,016
Additional paid-in capital	164,814,664	130,659,550
Accumulated deficit	(130,005,111)	(105,909,384)
Total stockholders' equity	34,911,467	24,814,182
Total liabilities and stockholders' equity	$ 37,839,151	$ 27,729,551

See accompanying notes to consolidated financial statements.

DIFFUSION PHARMACEUTICALS INC.

CONSOLIDATED STATEMENTS OF OPERATIONS

	Year Ended December 31,	
	2021	**2020**
Operating expenses:		
Research and development	$ 8,499,414	$ 9,427,667
Intangible asset impairment charge	8,639,000	—
General and administrative	7,445,277	6,444,109
Depreciation	93,416	103,168
Loss from operations	(24,677,107)	(15,974,944)
Other income:		
Interest income	137,487	114,257
Loss before income taxes	(24,539,620)	(15,860,687)
Income tax benefit	443,893	1,675,381
Net loss	$ (24,095,727)	$ (14,185,306)
Deemed dividend arising from warrant exchange	—	(1,950,378)
Net loss applicable to common stockholders	$ (24,095,727)	$ (16,135,684)
Share information:		
Net loss per share of common stock, basic and diluted	$ (0.25)	$ (0.30)
Weighted average shares outstanding, basic and diluted	97,626,748	53,831,973

See accompanying notes to consolidated financial statements.

DIFFUSION PHARMACEUTICALS INC.

CONSOLIDATED STATEMENTS OF CHANGES IN STOCKHOLDERS' EQUITY

	Stockholders' Equity				
	Common Stock				
	Shares	Amount	Additional Paid-in Capital	Accumulated Deficit	Total Stockholders' Equity
Balance at December 31, 2019	33,480,365	$ 33,481	$ 111,824,859	$ (91,724,078)	$ 20,134,262
Issuance of common stock, pre-funded warrants and warrants, net of issuance costs	11,428,572	11,429	10,330,202	—	10,341,631
Issuance of common stock upon exercise of warrants	19,106,504	19,106	7,768,370	—	7,787,476
Stock-based compensation expense	—	—	736,119	—	736,119
Net loss	—	—	—	(14,185,306)	(14,185,306)
Balance at December 31, 2020	64,015,441	64,016	130,659,550	(105,909,384)	24,814,182
Issuance of common stock and warrants, net of issuance costs	33,658,538	33,658	31,060,644	—	31,094,302
Issuance of common stock upon exercise of warrants	4,230,000	4,230	2,197,220	—	2,201,450
Vesting of restricted stock units	10,301	10	(10)	—	—
Stock-based compensation expense	—	—	897,260	—	897,260
Net loss	—	—	—	(24,095,727)	(24,095,727)
Balance at December 31, 2021	101,914,280	$ 101,914	$ 164,814,664	$ (130,005,111)	$ 34,911,467

See accompanying notes to consolidated financial statements.

DIFFUSION PHARMACEUTICALS INC.

CONSOLIDATED STATEMENTS OF CASH FLOWS

	Year Ended December 31,	
	2021	**2020**
Operating activities:		
Net loss	$ (24,095,727)	$ (14,185,306)
Adjustments to reconcile net loss to net cash used in operating activities:		
Depreciation and amortization	93,416	103,168
Loss on disposal of property and equipment	51,782	—
Stock-based compensation expense	897,260	736,119
Abandonment of in-process research and development intangible asset	8,639,000	—
Change in deferred income taxes	(443,893)	(1,675,381)
Changes in operating assets and liabilities:		
Prepaid expenses, deposits and other assets	(248,997)	518,169
Accounts payable, accrued expenses and other liabilities	605,370	950,602
Net cash used in operating activities	(14,501,789)	(13,552,629)
Cash flows provided by investing activities:		
Cash received from sale of property and equipment	4,000	—
Net cash provided by investing activities	4,000	—
Cash flows provided by financing activities:		
Proceeds from the sale of common stock, net of issuance costs	31,094,302	10,827,100
Proceeds from the sale of common stock warrants	2,201,450	8,046,103
Payment of offering costs	—	(982,328)
Net cash provided by financing activities	33,295,752	17,890,875
Net increase in cash and cash equivalents	18,797,963	4,338,246
Cash and cash equivalents at beginning of year	18,515,595	14,177,349
Cash and cash equivalents at end of year	$ 37,313,558	$ 18,515,595
Supplemental disclosure of non-cash investing and financing activities:		
Vesting of restricted stock units	$ 10	$ —

See accompanying notes to consolidated financial statements.

1. Organization and Description of Business

Diffusion Pharmaceuticals Inc. ("the Company"), a Delaware corporation, is a biopharmaceutical company developing novel therapies that enhance the body's ability to deliver oxygen to areas where it is needed most. The Company's lead product candidate, TSC, is being developed to enhance the diffusion of oxygen to tissues with low oxygen levels, also known as hypoxia, a serious complication of many of medicine's most intractable and difficult-to-treat conditions. In November 2021, based on the preclinical and clinical data accumulated to date and the significant unmet medical need, the Company announced that its near-term focus will be the design and execution of a clinical program to support the use of intravenously administered TSC as an adjunctive treatment for hypoxic solid tumors.

2. Liquidity

The Company has not generated any revenues from product sales and has funded operations primarily from the proceeds of public and private offerings of equity, 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 at all, 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. The Company 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 such arrangements or if it entered into such arrangements at later stages in the product development process.

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 expects that its existing cash and cash equivalents as of December 31, 2021 will enable it to fund its operating expenses and capital expenditure requirements through 2023.

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 GAAP. Any reference in these notes to applicable guidance is meant to refer to GAAP as found in the Accounting Standards Codification and Accounting Standards Updates of the Financial Accounting Standards Board.

Use of Estimates

The preparation of financial statements in conformity with 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 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 and accounts payable approximate fair value due to the short-term nature of those instruments.

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. In November 2021, the Company terminated the lease of its prior corporate headquarters and in connection with the termination the Company disposed of all of its related property and equipment.

Intangible Asset

In the third quarter of 2021, the Board of Directors made a determination to no longer dedicate financial resources to the Company's DFN-529 intangible asset and any future internal development efforts were abandoned. In connection with this decision, the Company concluded that DFN-529 was impaired in its entirety and as such, the Company recognized a non-cash impairment charge of $8.6 million during the third quarter of 2021. The abandonment also resulted in an income tax benefit of $0.4 million due to the tax effect of the reduction in the deferred tax liability associated with the asset.

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.

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 consolidated 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.

FASB ASC Subtopic 740-10, *Accounting for Uncertainty of Income Taxes*, ("ASC 740-10") defines the criterion an individual tax position must meet for any part of the benefit of the tax position to be recognized in financial statements prepared in conformity with GAAP. The Company may recognize the tax benefit from an uncertain tax position only if it is more likely than not such tax position will be sustained on examination by the taxing authorities, based solely on the technical merits of the respective tax position. The tax benefits recognized in the financial statements from such a tax position should be measured based on the largest benefit having a greater than 50% likelihood of being realized upon ultimate settlement with the tax authority. In accordance with the disclosure requirements of ASC 740-10, the Company's policy on income statement classification of interest and penalties related to income tax obligations is to include such items as part of total interest expense and other expense, respectively.

Stock-based Compensation

The Company measures stock-based awards at grant-date fair value and records compensation expense on a straight-line basis over the vesting period of the award. The Company uses the Black-Scholes 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.

For certain stock option grants, the expected term was estimated using the "simplified method" for employee options as the Company has limited 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. During the year ended December 31, 2020, it became apparent that the expected term of the Company's stock options was commensurate with the contractual life (i.e. 10 years) of the stock option and therefore the Company began to use the contractual life as the expected term.

For stock price volatility, the Company uses a combination of its own historical stock price and 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 term of the option. The Company accounts for forfeitures in the periods they occur.

Net Loss Per Common Share

Basic net 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. Diluted net loss per share includes the effect, if any, from the potential exercise or conversion of securities, such as convertible debt, convertible preferred stock, common stock warrants, stock options and unvested restricted stock that would result in the issuance of incremental shares of common stock. In computing the basic and diluted net loss per share applicable to common stockholders, the weighted average number of shares remains the same for both calculations due to the fact that when a net loss exists, dilutive shares are not included in the calculation as the impact is anti-dilutive.

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,	
	2021	**2020**
Common stock warrants	6,499,469	9,100,112
Stock options	3,626,223	2,240,204
Unvested restricted stock units	275,450	153,000
	10,401,142	11,493,316

Recently Issued But Not Yet Adopted Accounting Pronouncements

In June 2016, the FASB issued ASU 2016-13, Financial Instruments—*Credit Losses, Measurement of Credit Losses on Financial Instruments* (Topic 326). The standard amends the impairment model by requiring entities to use a forward-looking approach based on expected losses to estimate credit losses for most financial assets and certain other instruments that aren't measured at fair value through net income. For available-for-sale debt securities, entities will be required to recognize an allowance for credit losses rather than a reduction in carrying value of the asset. Entities will no longer be permitted to consider the length of time that fair value has been less than amortized cost when evaluating when credit losses should be recognized. This new guidance is effective for the Company as of January 1, 2022. The Company is currently evaluating the impact of this ASU but does not expect that adoption of this standard will have a material impact on its consolidated financial statements and related disclosures.

Recently Adopted Accounting Pronouncements

In December 2019, the FASB issued ASU No. 2019-12, "Income Taxes (Topic 740): *Simplifying the Accounting for Income Taxes*." This guidance applies to all entities and aims to reduce the complexity of tax accounting standards while enhancing reporting disclosures. This guidance is effective for fiscal years beginning after December 15, 2020 and interim periods therein. Early adoption is permitted for any annual periods for which financial statements have not been issued and interim periods therein. The Company adopted this standard in January 2021 and the adoption did not have a material impact on its related disclosures.

4. Accrued Expenses and Other Current Liabilities

Accrued expenses and other current liabilities consist of the following:

	December 31,	
	2021	2020
Accrued payroll and payroll related expenses	$ 879,971	$ 653,899
Accrued professional fees	247,704	31,809
Accrued clinical studies expenses	786,579	1,055,398
Other	65,935	35,364
Total	$ 1,980,189	$ 1,776,470

5. Commitments and Contingencies

Office Space Lease Commitment

On November 8, 2021, the Company entered into a Deed of Lease Termination Agreement with the Carlton Landlord providing for the early termination of the Carlton Lease related to the Company's prior corporate headquarters. The Carlton Lease was previously scheduled to expire on April 30, 2022. In connection with the termination, the Company made a one-time payment to the Carlton Landlord of approximately $14,000, net of a security deposit subsequently returned in accordance with the Carlton Lease. In lieu of the fixed office and laboratory space previously available to us under the Carlton Lease, the Company has entered into short term agreements to utilize membership-based co-working space in both Charlottesville, Virginia and Philadelphia, Pennsylvania.

Rent expense related to the Company's operating lease for both the years ended December 31, 2021 and 2020 was approximately $0.1 million.

Research and Development Arrangements

In the course of normal business operations, the Company enters into agreements with universities and contract research organizations, or CROs, to assist in the performance of research and development activities and contract manufacturers to assist with chemistry, manufacturing, and controls related expenses. Expenditures to CROs represent a significant cost in clinical development for the Company. The Company could also enter into additional collaborative research, contract research, manufacturing, and supplier agreements in the future, which may require upfront payments and long-term commitments of cash.

Defined Contribution Retirement Plan

The Company has established a 401(k) defined contribution 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 $75,000 and $68,000 for the years ended December 31, 2021 and 2020, respectively.

Legal Proceedings

On August 7, 2014, a complaint was filed in the Superior Court of Los Angeles County, California by Paul Feller, the former Chief Executive Officer of the Company's legal predecessor 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 related hearing 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 was scheduled, originally for November 2020 but later postponed due to the COVID-19 pandemic and related restrictions on gatherings in the State of California. In addition, following the November 2018 hearing, an automatic stay was placed on the arbitration in connection with the plaintiff filing for personal bankruptcy protection. On October 22, 2021, following a determination by the bankruptcy trustee not to pursue the claims and release them back to the plaintiff, the parties entered into a stipulation to abandon arbitration and return the matter to state court. A case management conference was held on February 23, 2022 at which a trial date of May 24, 2023 was set, and the parties have agreed to stipulate to mediation in advance of the trial.

The Company believes the claims in this matter are without merit and intends to defend itself vigorously. However, at this stage, the Company is unable to predict the outcome and 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, results of operations and cash flows.

6. Stockholders' Equity and Common Stock Warrants

2021 Common Stock Offering

In February 2021, the Company completed the February 2021 Offering in which it offered and sold 33,658,538 shares of its common stock in an underwritten, public offering for a purchase price to the public of $1.025 per share, inclusive of shares offered and sold pursuant to the exercise in full by the underwriter of its 30-day option to purchase additional shares. The February 2021 Offering resulted in aggregate net proceeds to the Company of $31.1 million, after deducting underwriting commissions, discounts, and expenses. In addition, at the closings of the February 2021 Offering, the Company issued to designees of the underwriter of the transaction warrants to purchase up to an aggregate of 1,682,927 shares of common stock to designees. The underwriter warrants have an exercise price of $1.28125 per share and a term of five years from the date of issuance.

2020 Common Stock Offering

In May 2020, the Company completed the May 2020 Offering, a public offering of 11,428,572 shares of common stock for a purchase price of $1.05 per share for net proceeds of $10.3 million after deducting commissions, discounts, and other offering costs. In addition, at the closing of the May 2020 Offering, the Company issued warrants to purchase up to 571,429 shares of common stock to designees of the placement agent for the May 2020 Offering. The placement agent's warrants have an exercise price of $1.3125 per share and a term of five years from the date of issuance.

Additionally, also in May 2020, the Company entered into a warrant exercise agreement with an investor who held the Prior Warrant, a previously outstanding warrant to purchase up to an aggregate of 5,000,000 shares of our common stock at an exercise price of $0.35 per share. In consideration for the exercise of the Prior Warrant for cash and an additional $0.125 per each share of common stock in the Prior Warrant being exercised, the exercising investor received new unregistered warrants to purchase up to an aggregate of 5,000,000 shares of common stock in a private placement. The warrants are exercisable immediately at an exercise price of $0.5263 per share and exercisable until November 8, 2025. During the year ended December 31, 2020, the Company recognized a deemed dividend of $2.0 million to reflect the consideration given as an inducement for the investor to exercise the warrants. This deemed dividend was recorded in the Company's consolidated statement of operations during the year ended December 31, 2020 as an increase to the net loss applicable to common stockholders for purposes of computing net loss per share, basic and diluted.

In connection with the May 2020 Investor Warrant Exercise, the Company issued warrants to purchase up to 250,000 shares of common stock to the placement agent with an exercise price of $0.5938 per share and otherwise have identical terms to the warrants issued to the investor.

Common Stock Warrants

During its evaluation of equity classification for the Company's common stock warrants issued in 2020 and 2019, the Company considered the conditions as prescribed within ASC 815-40, *Derivatives and Hedging, Contracts in an Entity's own Equity*. 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.

As of December 31, 2021, 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 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 January 2018 common stock offering	1,181,421	$12.00 - $15.00	January 2023
Common stock warrants issued related to the May 2019 Offering	1,382,913	$5.00 - $6.11875	May and December 2024
Common stock warrants issued related to the November 2019 Offering	213,570	$0.35	May 2024
Common stock warrants issued related to the December 2019 Offering	313,339	$0.6981	December 2024
Common stock warrants issued related to the May 2020 Offering	571,429	$1.3125	March 2025
Common stock warrants issued related to the May 2020 Investor Warrant Exercise	250,000	$0.5938	November 2025
Common stock warrants issued related to the February 2021 Offering	1,682,927	$1.28	February 2026
	6,499,469		

During the year ended December 31, 2021, 53,570 warrants expired and 4,230,000 warrants were exercised for proceeds of approximately $2.2 million. During the year ended December 31, 2020, no warrants expired and 19,106,504 warrants were exercised for gross proceeds of $8.0 million.

7. Stock-Based Compensation

2015 Equity Plan

The 2015 Equity Plan provides for increases to the number of shares reserved for issuance thereunder each January 1 equal to 4.0% of the total shares of the Company's common stock outstanding as of the immediately preceding December 31, unless a lesser amount is stipulated by the Compensation Committee of the Company's board of directors. Accordingly, 4,076,571 shares were added to the reserve as of January 1, 2022. All such shares may be issued 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, in each case, in accordance with the terms of the 2015 Equity Plan. As of December 31, 2021, there were 580,925 shares of common stock available for future issuance under the 2015 Equity Plan. Generally, the options have a ten (10) year contractual term and vest in equal monthly installments over three (3) years.

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,	
	2021	2020
Research and development	$ 154,041	$ 164,791
General and administrative	743,219	571,328
Total stock-based compensation expense	$ 897,260	$ 736,119

The following table summarizes the activity related to all stock options:

	Number of Options	Weighted average exercise price per share	Weighted average remaining contractual life (in years)	Aggregate Intrinsic Value
Balance at January 1, 2020	309,276	$ 55.78		
Granted	1,931,100	0.68		
Expired	(172)	142.50		
Balance at December 31, 2020	2,240,204	$ 8.28		$ 289,067
Granted	1,815,767	0.89		
Forfeited	(429,748)	1.37		
Outstanding at December 31, 2021	3,626,223	5.40	8.52	—
Exercisable at December 31, 2021	2,140,524	$ 8.58	8.09	—
Vested and expected to vest at December 31, 2021	3,626,223	$ 5.40	8.52	—

The weighted average grant date fair value of stock option awards granted was $0.89 and $0.64 during the years ended December 31, 2021 and 2020, respectively. The total fair value of options vested during the years ended December 31, 2021 and 2020 were $0.8 million and $0.7 million, respectively. No options were exercised during any of the periods presented. At December 31, 2021, there was $1.1 million of unrecognized compensation cost related to unvested options that will be recognized as expense over a weighted-average period of 1.7 years. During the year ended December 31, 2021, the Company granted 385,267 performance-based stock options with an exercise price of $1.11 per share, subject to vesting based on the satisfaction of specified performance criteria. Compensation expense for the performance-based awards is recorded over the estimated service period for each milestone when the performance conditions are deemed probable of achievement. The Company recorded stock-based compensation expense of approximately $0.1 million year ended December 31, 2021, for service-based awards with performance conditions deemed probable of achievement and/or achieved. For performance-based awards containing performance conditions which were not deemed probable of achievement at December 31, 2021, no stock compensation expense was recognized and any previously recognized expense related to those awards originally deemed probable was reversed.

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, 2021 and 2020:

	2021	2020
Expected term (in years)	10	5.31 — 10
Risk-free interest rate	1.3% — 1.7%	0.4% — 1.7%
Expected volatility	122.6% — 125.8%	113.4% — 124.8%
Dividend yield	0%	0%

Restricted Stock Unit Awards

The Company issues restricted stock ("RSU") to newly elected, non-executive members of the board of directors that vest in six, tri-monthly installments beginning 18 months after the respective grant date. The fair value of a RSU is equal to the fair market value price of the Company's common stock on the date of grant. RSU expense is recorded on a straight-line basis over the service period.

The following table summarizes activity related to RSU stock-based payment awards:

	Number of Units	Weighted average grant date fair value
Balance at January 1, 2021	153,000	$ 0.65
Granted	138,800	0.72
Vested(1)	(16,350)	0.51
Outstanding at December 31, 2021	275,450	$ 0.70

(1) The Company withheld 6,049 shares of common stock to cover the tax liability associated with the vesting of these units in 2021.

The Company recognized approximately $54,000 and $18,000 in expense related to these units during the years ended December 31, 2021 and December 2020, respectively. At December 31, 2021, there was approximately $0.1 million of unrecognized compensation cost that will be recognized over a weighted average period of 2.12 years.

8. 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, 2021**	**December 31, 2020**
Net operating loss carryforwards	$ 6,033,726	$ 3,864,189
Stock option compensation	1,641,354	1,571,227
Orphan Drug credits	647,937	541,384
Lease liability	—	38,394
Capitalized start-up costs and other	12,403,925	10,709,631
Valuation allowance	(20,726,942)	(14,906,646)
Deferred tax assets	—	1,818,179
Deferred tax liabilities		
Intangible assets	—	(2,223,678)
Right of use asset	—	(38,394)
Deferred tax liabilities	—	(2,262,072)
Net deferred tax liability	$ —	$ (443,893)

The Company does not have unrecognized tax benefits as of December 31, 2021 or December 31, 2020. The Company recognizes interest and penalties accrued on any unrecognized tax benefits as a component of income tax expense.

The Company had NOL carryforwards for federal and state income tax purposes at December 31, 2021 and 2020 of approximately:

Combined NOL Carryforwards:	**December 31, 2021**	**December 31, 2020**
Federal	$ 23,442,045	$ 15,013,388
State	23,436,624	15,007,966

The pre-2018 net operating loss carryforwards begin expiring in 2021 for both federal and state income tax purposes. In November 2019, 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. 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. The Company recorded a 100% valuation allowance of the deferred tax assets as of December 31, 2021 because of the uncertainty of their realization.

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

Rate reconciliation:	**December 31, 2021**	**December 31, 2020**
Federal tax benefit at statutory rate	(21.0)%	(21.0)%
State tax, net of Federal benefit	(4.7)%	(4.7)%
Orphan drug credit	(0.4)%	(2.9)%
Change in valuation allowance	24.3%	18.1%
Total provision	(1.8)%	(10.5)%

The Company files income tax returns in the U.S. federal jurisdiction and various state jurisdictions. The Company's 2018 to 2021 tax years remain open and subject to examination. All net operating losses and credits remain subject to review until utilized.

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 Exchange Act 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 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, 2021.

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. As a "smaller reporting company" (as such term is defined in Rule 12b-2 of the Exchange Act), pursuant to Section 989G of the Dodd-Frank Act, we are exempt from the requirement subjecting management's report to attestation by our independent registered public accounting firm.

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, 2021 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

CORPORATE GOVERNANCE

Introduction

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 Capital Market, the Board has adopted certain governance standards, including its standard of independence.

Corporate Governance Guidelines

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

Directors & Director Independence

The Board has determined that six of our seven current directors — Robert Adams, Eric Francois, Mark T. Giles, Jane H. Hollingsworth, Diana Lanchoney, and Alan Levin — are "independent directors" under the Listing Rules of the Nasdaq Capital Market.

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, Jane H. Hollingsworth serves as the Chair of the Board and Robert J. Cobuzzi, Jr. serves as our Chief Executive Officer. The Board believes that it is currently in the best interests of the Company's stockholders to separate these offices. This separation allows for our Board Chair to act as a bridge between the Board and the operating organization, while our Chief Executive Officer focuses on running the Company's business. The Board believes that this separation allows for a more effective utilization of the proven leadership capabilities, breadth of industry experience and business success of the individuals holding both positions, and that the Company and its stockholders are best currently served by this leadership structure.

Executive Sessions

Generally, at regular meetings of the Board, our independent directors meet in executive session with no company management present during a portion of the meeting. Ms. Hollingsworth typically presides over these executive sessions and serves as a liaison between the independent directors and our Chief Executive Officer.

Board Meetings and Attendance

During 2021, the Board held nine meetings, including one joint meeting with the Compensation Committee. Each of our directors attended 75 percent or more of the meetings of the Board and all committees on which he or she served during 2021. In addition, the Company's directors are expected to participate in the annual meetings of stockholders, and all of the Company's directors participated in the 2021 annual meeting of stockholders.

Board Committees

The Board has three standing committees: the Audit Committee, the Compensation Committee, and the 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 the Company and may change the composition and the responsibilities of the existing committees. Each of the 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.

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 advisors 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. Francois, Giles, and Levin and Ms. Hollingsworth. 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 Capital Market and the rules and regulations of the SEC and is "financially literate" under the Listing Rules of the Nasdaq Capital 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 Capital 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 Capital 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 five times during 2021.

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, Mr. 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; and
- establishing and leading a process for determination 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 advisors as it deems necessary or appropriate to carry out its duties and responsibilities.

Composition

The current members of the Compensation Committee are Messrs. Adams and Francois, Ms. Hollingsworth, and Dr. Lanchoney. Mr. Adams is the chair of the Compensation Committee. Each of the four current members of the Compensation Committee is an "independent director" under the Listing Rules of the Nasdaq Capital Market and a "non-employee director" within the meaning of Rule 16b-3 under the Exchange Act.

Meetings

The Compensation Committee met seven times during 2021, including one joint meeting with the Board.

Processes and Procedures for Consideration and Determination of Executive Compensation

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; and the executive's current and historical compensation levels. The Compensation Committee has also from time to time – including during 2021 – retained the services of its independent consulting firm, Radford, to provide advice with respect to executive compensation, such as developing a group of comparable peer companies and reviewing executive and director compensation levels. In making decisions regarding the form and amount of compensation to be paid to our executives, the Compensation Committee may consider information gathered by, and the recommendations of, Radford, when necessary and appropriate.

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 about the Chief Executive Officer without the presence of the Chief Executive Officer or any executive or employee of our company.

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 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, including the recommendations of Radford, when necessary and appropriate.

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;
- general management and director succession planning;
- 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;
- developing and overseeing a Board and Board committee evaluation process; and
- reviewing and discussing with our Chief Executive Officer and reporting periodically to the Board plans for executive officer development and succession plans for the Chief Executive Officer and other key executive officers and employees; and

The Nominating and Corporate Governance Committee has the authority to engage the services of outside experts and advisors 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 and Dr. Lanchoney. Mr. Giles is the chair of the Nominating and Corporate Governance Committee. Each of the four current members of the Nominating and Corporate Governance Committee is an "independent director" within the meaning of the Listing Rules of the Nasdaq Capital Market.

Meetings

The Nominating and Corporate Governance Committee met three times during 2021.

Processes and Procedures for Consideration Director Nominations

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 certain 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 (including with respect to diversity), 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 described 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 for purposes of serving as a member of the Audit Committee;
- 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, in general and as compared to other directors on the Board; 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 described above. 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 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, our processes for the management of business and financial risk, our financial reporting obligations, and our 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. The Nominating and Corporate Governance Committee oversees risks relating to our corporate governance matters and policies and management 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 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.

Policy Regarding Director Attendance at Annual Meetings of Stockholders

It is the policy of the Board that directors standing for re-election should attend our annual meeting of stockholders, if their schedules permit.

Process Regarding Stockholder Communications with Board

Stockholders may communicate with the Board or any one particular director by sending correspondence, to our General Counsel & Corporate Secretary via e-mail to info@diffusionpharma.com or via mail to 300 East Main Street, Suite 201, Charlottesville, Virginia 22902, with an instruction to forward the communication to the Board or one or more particular directors. Our General Counsel & Corporate Secretary will forward promptly all such stockholder communications to the Board or the one or more particular directors, with the exception of any advertisements, solicitations for periodical or other subscriptions and other similar communications.

DIRECTORS

Number of Directors

Our Bylaws provide that the Board will consist of at least one member, or such other number as may be determined by the Board or our stockholders. The Board has currently fixed the number of directors at seven.

Information About Our Directors

The table below sets forth, as of March 15, 2022, certain information that has been furnished to us by our current directors.

Name	Age	Director Since
Robert Adams	71	2016
Robert J. Cobuzzi, Jr., Ph.D.	57	2020
Eric Francois	47	2021
Mark T. Giles	67	2016
Jane H. Hollingsworth	63	2020
Diana Lanchoney, M.D.	55	2021
Alan Levin	59	2016

In addition, the paragraphs below provide further information about each current director, including all positions he or she holds, his or her principal occupation and business experience for the past five years, and the names of other publicly held companies of which he or she currently serves as a director or served as a director during the past five years. We believe that all of our directors and 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 and nominee for 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.

Robert Adams — Mr. Adams has served as a director since January 2016 and as a director of Diffusion LLC since 2002. Prior to his retirement in 2015, Mr. Adams was a partner in the intellectual property law firm of Nixon & Vanderhye 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.

Robert J. Cobuzzi, Jr., Ph.D. – Dr. Cobuzzi has served as a director since January 2020 and as our President and Chief Executive Officer since September 2020. Cobuzzi also currently serves as a Venture Partner and Chairman of the Business Development Board for Sunstone Life Science Ventures, an early-stage, European-focused investor in human therapeutics. He also serves on behalf of Sunstone as a Board Observer for Synendos Therapeutics, a venture-backed, Swiss-based biopharmaceutical company focused on developing therapeutics for neuropsychiatric disorders. Previously, Dr. Cobuzzi served as an Advisor to the Mitochondrial Disease Research Program at the Children's Hospital of Philadelphia, an internationally recognized hospital and research center devoted to children, from January 2019 to April 2020, and as President and Chief Executive Officer of MitoCUREia, Inc., an affiliated company, from July 2019 to July 2020. From 2005 to 2018, Dr. Cobuzzi served in various roles at Endo International PLC, a specialty branded and generic pharmaceuticals manufacturer, most recently serving as President of Endo Ventures Ltd. Dr. Cobuzzi received his Bachelor of Arts in Biochemistry and Art History from Colby College and his Ph.D. in Molecular and Cellular Biochemistry from Loyola University Chicago. He served as a Post-doctoral Fellow in Experimental Therapeutics at Roswell Park Cancer Institute.

The Board believes Dr. Cobuzzi's experience and insight with drug development and business development and funding, both in the U.S. and abroad, as well as his experience and background as our Chief Executive Officer, provide him with the qualifications to serve as a director.

Eric Francois – Mr. Francois has served as a director since June 2021. Since November 2021, Mr. Francois has served as a Managing Director at the investment banking firm of Credit Suisse. From November 2015 until November 2021, Mr. Francois served as Chief Financial Officer of Scynexis, Inc., a pharmaceutical company pioneering innovative medicines to potentially help millions of patients worldwide in need of new options to overcome and prevent difficult-to-treat and drug-resistant infections. He previously served as co-founder and Chief Operating Officer of Topi, Inc., a technology startup, from July 2013 to October 2015, where he was responsible for all marketing, commercial and financial activities and helped grow the company from inception to over 250 clients worldwide. Previously, Mr. Francois served from September 2007 to July 2013 as a Director in the Equity Capital Markets Group at Lazard Ltd where he led capital raisings and advisory assignments for healthcare and biotechnology companies. He started his career in September 2000 at Cowen and Company in the Equity Capital Markets and Convertible Debt Groups. Mr. Francois holds a B.A. in Economics and Business Administration and a M.A. in Marketing from Pantheon-Sorbonne University, France.

The Board believes that the combination of Mr. Francois's perspective and industry experience, his experience in financial reporting, corporate finance, and capital raising transactions, and his executive-level experience in the pharmaceutical industry all provide him with the qualifications and skills 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 since 2008. Since July 2007, Mr. Giles has been the sole managing member of Panda Holdings, LLC, which engages in the investment and management of private capital. Since February 2015, Mr. Giles has been a general partner of Anchormark Holdings, LLC, which engages in the investment and management of private capital. Prior to joining Panda Holdings and Anchormark Holdings, 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 also 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. 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.

Jane H. Hollingsworth – Ms. Hollingsworth has served as a director since September 2020. She currently serves as the founding Managing Partner of Militia Hill Ventures, an organization that creates, builds, and invests in life sciences companies, a role she has held since 2013. While at Militia Hill, Jane co-founded and currently serves as Executive Chair of Eliksa Therapeutics, a regenerative medicine company, co-founded and served as Executive Chair of Spirovant Sciences, a gene therapy company sold to Sumitomo Dainippon Pharma, and served as Executive Chair and CEO of Immunome Inc., a cancer immunotherapy company. Prior to founding Militia Hill, Ms. Hollingsworth co-founded and served as Chief Executive Officer of NuPathe, Inc., a neuroscience focused biopharmaceutical company. . She also co-founded and served as EVP of Auxilium Pharmaceuticals, a urology and rare disease focused biopharmaceutical company. Ms. Hollingsworth also currently serves on the board of various industry and community organizations, including Afimmune Ltd., Ribonova, the University City Science Center, the Kimmel Center for the Performing Arts and Breatcancer.Org. Ms. Hollingsworth received her B.A. from Gettysburg College and her J.D. from Villanova University.

The Board believes Ms. Hollingsworth's industry perspective and experience, including as chief executive officer and director of a publicly-traded biopharmaceutical company, as well as her depth of her other operating and senior management experience in our industry and educational background, provide her with the qualifications to serve as a director.

Diana Lanchoney, M.D. – Dr. Lanchoney has served as a director since June 2021. Since 2014, Dr. Lanchoney has served as a Vice President of CSL Behring, Inc., a global biopharmaceutical company manufacturing plasma-derived and recombinant therapeutic products, since October 2021 as Vice President, R&D Strategy Implementation, from January 2018 to October 2021 as Vice President, Clinical Pharmacology and Translational Development and prior to that as Vice President, R&D Project Management, from October 2014 to December 2017. Prior to joining CSL, Dr. Lanchoney served in positions of increasing responsibility with Merck & Co., a global pharmaceutical company, most recently as Associate Vice President, Corporate Strategy. Dr. Lanchoney received her B.A. in Economics and German Studies from Tufts University and her M.D. from the University of Pennsylvania.

The Board believes Dr. Lanchoney's professional and academic background and experience provide her with the qualifications to serve as a director, including the depth and breadth of her experience with clinical development, corporate strategy, and pharmaceutical industry partnering.

Alan Levin — Mr. Levin has served as a director since January 2016 and as a director of Diffusion LLC since June 2015. He previously served as Executive Vice President and Chief Financial Officer of Endo Health Solutions Inc., 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. Mr. Levin currently serves as a member of the board of directors of Biocryst Pharmaceuticals, Inc., a Nasdaq-traded biopharmaceuticals company. He is also a member of the Advisory Board of Auven 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. From December 2013 to July 2019, he was a member of the board of directors of Aceto Corporation, a Nasdaq-traded company specialized in generics and pharmaceutical intermediate products.

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.

Overview of Non-Employee 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. Dr. Cobuzzi, our Chief Executive Officer, is not compensated separately for serving on the Board while also serving as an employee.

As further described below, the principal elements of our non-employee director compensation program for 2021 included cash compensation in the form of annual cash retainers and long-term equity-based incentive compensation, in the form of stock options and restricted stock units.

Cash Compensation

The cash compensation paid to our non-employee members of the Board consists of the following cash retainers:

Description	Annual Cash Retainer	
Board Member	$	40,000
Chair of the Board	$	25,000
Audit Committee Chair	$	15,000
Compensation Committee Chair	$	10,000
Nominating and Corporate Governance Committee Chair	$	8,000
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)	$	4,000

The annual cash retainers are paid in regular installments and otherwise 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 2021, 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 and restricted stock units. Upon a non-employee director's initial appointment to the Board, he or she shall receive a stock option award to purchase a number of shares of common stock equal to 0.114% of our shares of common stock outstanding on the grant date, vesting in 18 equal monthly installments following his or her appointment to the Board. In addition, upon appointment he or she also receives a restricted stock unit award for an equivalent number of shares, vesting in six tri-monthly installments commencing on the 18-month anniversary of his or her appointment to the Board. Directors appointed prior to January 1, 2020 received the entirety of this initial appointment award in the form of an option.

In addition, each non-employee director annually receives a stock option award to purchase a number of shares of common stock equal to 0.114% of our shares of common stock outstanding on the grant date, vesting in equal monthly installments over one year, unless otherwise provided by the Compensation Committee.

All option awards granted to our non-employee directors have a ten-year term and an exercise price equal to the fair market value of our common stock on the grant date.

Director Compensation Table for 2021

The table below provides summary information concerning the compensation of each individual who served as a non-employee director of the Company during the year ended December 31, 2021:

Name	Fees Earned or Paid in Cash	Stock Awards (1)	Option Awards (2)	All Other Compensation	Total
Robert Adams	$ 57,616	$ -	$ 57,084	$ -	$ 114,700
Robert J. Cobuzzi, Jr., Ph.D. (3)	$ 0	$ -	$ 170,735(3)	$ 612,617(3)	$ 783,352
Eric Francois (4)	$ 27,185	$ 49,968	$ 114,167	$ -	$ 141,352
John L. Gainer, Ph.D. (4)	$ 19,288	$ -	$ -	$ -	$ 19,288
Mark T. Giles	$ 57,911	$ -	$ 57,084	$ -	$ 114,995
Jane H. Hollingsworth	$ 67,374	$ -	$ 57,084	$ -	$ 124,458
David G. Kalergis (4)	$ 28,932	$ -	$ -	$ -	$ 28,932
Diana Lanchoney (4)	$ 25,373	$ 49,968	$ 114,167	$ -	$ 139,540
Alan Levin	$ 61,411	$ -	$ 57,084	$ -	$ 118,495

1) The amounts shown in this column reflect the grant date fair value of restricted stock unit awards granted during 2021 to the identified directors upon their respective initial appointments to the Board, calculated in accordance with the provisions of ASC Topic 718 and determined without regard to forfeitures. See the assumptions used in the Black-Scholes Model in Note 7 to the audited financial statements included in our Annual Report. As of December 31, 2021, the aggregate number of shares underlying restricted stock units granted to our directors were as follows: Dr. Cobuzzi – 98,100, 16,350 of which were vested; Mr. Francois – 69,400, none of which were vested; Ms. Hollingsworth – 54,900, none of which were vested; and Dr. Lanchoney – 69,400, none of which were vested.

2) The amounts shown in this column reflect the grant date fair value of option awards granted during 2021 to the identified directors and former directors, calculated in accordance with the provisions of ASC Topic 718 and determined without regard to forfeitures. See the assumptions used in the Black-Scholes Model in Note 7 to the audited financial statements included in our Annual Report. As of December 31, 2021, the aggregate number of shares subject to options awarded to our each of our directors and former directors were as follows: Mr. Adams – 177,745, of which 136,125 were vested; Dr. Cobuzzi – 761,726, of which 410,041 were vested; Dr. Gainer – 258,770, of which 258,770 were vested; Mr. Francois – 166,600, of which 69,417 were vested; Mr. Giles – 177,191, of which 135,541 were vested; Ms. Hollingsworth – 150,700, of which 101,562 were vested; Mr. Kalergis – 291,592, of which 291,592 were vested; Dr. Lanchoney – 166,600, of which 69,417 were vested; and Mr. Levin –176,557, of which 134,907 were vested.

3) Reflects compensation for Dr. Cobuzzi's service as our President and Chief Executive Officer. See "*Item 11. Executive Compensation -- Summary Compensation Table*" for additional information. Dr. Cobuzzi does not receive any additional compensation for his service as a director.

4) Dr. Gainer and Mr. Kalergis did not stand for re-election to the Board at our 2021 annual meeting of stockholders and their service on the Board ended upon Mr. Francois' and Dr. Lanchoney's election to the Board at such meeting on June 25, 2021.

EXECUTIVE OFFICERS

Information About Our Executive Officers

The table below sets forth, as of March 15, 2022, certain information concerning our executive officers. Biographical information for Dr. Cobuzzi is included above under the heading, “Directors — Information About Our Directors," and incorporated herein by reference.

Name	Age	Position with Diffusion
Robert J. Cobuzzi, Jr., Ph.D.	57	President and Chief Executive Officer
William K. Hornung	53	Chief Financial Officer
Christopher D. Galloway, M.D.	51	Chief Medical Officer
William R. Elder	39	General Counsel & Corporate Secretary

In addition, the paragraphs below provide further information about each current director, including all positions he or she holds, his or her principal occupation and business experience for the past five years, and the names of other publicly held companies of which he or she currently serves as a director or served as a director during the past five years.

William K. Hornung – Mr. Hornung serves as our Chief Financial Officer, a position he has held since September 2018. Prior to his appointment as Chief Financial Officer, 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.

Christopher D. Galloway, M.D. – Dr. Galloway has served as our Chief Medical Officer since October 2020. Prior to joining Diffusion, Dr. Galloway served as senior medical director in critical care for La Jolla Pharmaceutical Company from August 2018 to September 2020, where he chaired and oversaw La Jolla’s investigator-initiated and collaborative research programs and supported the commercial and medical teams in connection with the launch of GIAPREZA™ (angiotensin II), which has been approved by the U.S. Food and Drug Administration as a vasoconstrictor to increase blood pressure in adults with septic or other distributive shock. Prior to his time at La Jolla, Dr. Galloway served as medical director for global clinical development at Rakuten Medical Inc. (f/k/a Aspyrian Therapeutics, Inc.), a biotechnology company developing cell-targeting investigative immuno-oncology therapies, from December 2016 to July 2018 and as medical affairs director within Merck & Co., Inc.’s immunotherapy division from August 2015 to November 2016. Dr. Galloway received his doctor of medicine from the University of Texas Medical Branch at Galveston, completed his residency in emergency medicine at Carolinas Medical Center in Charlotte, NC, and received a B.A. in biology from the University of Texas at Austin. He is licensed to practice medicine in the State of Colorado and is a diplomate of the American Board of Emergency Medicine.

William R. Elder – Mr. Elder has served as our General Counsel & Corporate Secretary since September 2020. Prior to joining Diffusion, Mr. Elder principally served as president and chief executive officer of BillyVonElds, LLC, a season-long and daily fantasy sports company, where he managed all corporate, legal, and operational aspects of the business from April 2019 to September 2020. From July 2020 to September 2020, Mr. Elder also served as a part-time consultant to Diffusion. From 2011 to February 2019, Mr. Elder served as a corporate and securities associate for Dechert LLP, an international law-firm, where Mr. Elder’s practice focused primarily on counseling public companies on securities laws and regulatory requirements, corporate governance matters, and financial transactions in the equity and debt markets. He received his J.D. from the University of Pennsylvania Law School, an M.S. in finance from Villanova University, and a B.A. in economics from Tufts University.

ITEM 11. EXECUTIVE COMPENSATION

Summary Compensation Table

The table below provides summary compensation information concerning compensation awarded for service during the years ended December 31, 2021 and December 31, 2020 to the individuals that served as our named executive officers during the year ended December 31, 2021.

Name and Principal Position	Year	Salary (1)	Bonus Compensation (2)	Stock Awards (3)	Option Awards (4)	All Other Compensation (5)	Total
Robert J. Cobuzzi, Jr., Ph.D. (6)	2021	$ 410,000	$ 164,000	$ -	$ 170,735	$ 38,617	$ 783,352
Chief Executive Officer	2020	$ 129,046	$ 67,650	$ 50,031	$ 512,233	$ 58,535	$ 817,495
William K. Hornung	2021	$ 324,929	$ 96,667	$ -	$ 84,838	$ 29,084	$ 535,518
Chief Financial Officer	2020	$ 298,100	$ 93,902	$ -	$ 130,083	$ 17,866	$ 539,951
Christopher D. Galloway, M.D. (6)	2021	$ 375,000	$ 127,500	$ -	$ 86,393	$ 37,092	$ 625,985
Chief Medical Officer	2020	$ 66,827	$ 37,500	$ -	$ 190,882	$ 4,599	$ 299,808
William R. Elder (6)	2021	$ 256,250	$ 76,234	$ -	$ 66,246	$ 5,877	$ 404,607
General Counsel	2020	$ 68,270	$ 24,750	$ -	$ 147,429	$ 25,266	$ 265,715

1) Represents cash portion of base salary as described below under "*—Employment Agreements*."

2) Represents the annual cash incentive bonuses for service during the applicable year by our named executive officers as described further below under "*—2021 Bonus Compensation*".

3) The amount shown in this column reflects the grant date fair value of a restricted stock unit award made to Dr. Cobuzzi in connection with his initial appointment to the Board in January 2020, calculated in accordance with the provisions of ASC Topic 718 and determined without regard to forfeitures. The assumptions used in the Black-Scholes model are disclosed in Note 7 to the audited financial statements included in this Annual Report.

4) The amounts shown in this column reflect the grant date fair value of option awards granted for service during the applicable year, calculated in accordance with the provisions of ASC Topic 718 and determined without regard to forfeitures. Amounts shown for 2020 include time-based awards for service during 2020 granted in March 2021 and (i) with respect to Dr. Cobuzzi, $49,971 granted in January 2020 in connection with his initial appointment to the Board, $50,867 granted in June 2020 in connection with his service as a non-employee director during 2020, and $354,483 granted in September 2020 in connection with his initial appointment as Chief Executive Officer; (ii) with respective to Dr. Galloway, $162,083 granted in October 2020 in connection with his initial appointment as Chief Medical Officer, and (iii) with respect to Mr. Elder, $54,523 granted in September 2020 in connection with his initial appointment as General Counsel. Amounts shown for 2021 include the full grant date fair value of milestone-based, performance awards also granted in March 2021. Pursuant to the terms of the corresponding award agreements, two-thirds of the underlying shares originally granted were automatically forfeited due to the first patient in the ILD-DLCO Trial not being dosed on or before September 30, 2021. The Company announced dosing of the first patients in the ILD-DLCO Trial on December 16, 2021.

5) The amounts reported in this column for 2020 represent (w) with respect to Dr. Cobuzzi, (i) $50,076 in fees for his service as a non-employee director from January 2020 to September 2020 prior to his appointment as Chief Executive Officer in September 2020 (including fees for committee service), (ii) $5,162 in 401(k) Plan matching contributions by the Company, and (iii) $3,297 in Company-paid health insurance premiums, (x) with respect to Mr. Hornung, (i) $6,459 in 401(k) Plan matching contributions by the Company and (ii) $11,407 in Company-paid health insurance premiums, (y) with respect to Dr. Galloway, (i) $2,500 in 401(k) Plan matching contributions by the Company and (ii) $2,099 in Company-paid health insurance premiums, and (z) with respect to Mr. Elder, (i) $24,775 in fees for his service as a consultant to the Company from July 2020 to September 2020 prior to his appointment as General Counsel & Corporate Secretary and (ii) $491 in Company-paid health insurance premiums. The amounts reported in this column for 2021 represent (w) with respect to Dr. Cobuzzi, (i) $11,600 in 401(k) Plan matching contributions by the Company and (iii) $27,017 in Company-paid health insurance premiums, (x) with respect to Mr. Hornung, (i) $11,600 in 401(k) Plan matching contributions by the Company and (ii) $17,484 in Company-paid health insurance premiums, (y) with respect to Dr. Galloway, (i) $11,600 in 401(k) Plan matching contributions by the Company and (ii) $25,492 in Company-paid health insurance premiums, and (z) with respect to Mr. Elder, $5,877 in Company-paid health insurance premiums.

6) Dr. Cobuzzi began his employment as President & Chief Executive Officer on September 8, 2020 and began his service as a director on January 7, 2020, Dr. Galloway began his employment as Chief Medical Officer on October 19, 2020, and Mr. Elder began his employment as General Counsel & Corporate Secretary on September 23, 2020. Accordingly, during 2020, each received pro-rated compensation in accordance with his respective term of service.

Employment Agreements

Robert J. Cobuzzi, Jr., Ph.D., President & Chief Executive Officer

Effective September 8, 2020, we entered into an employment agreement with Dr. Cobuzzi pursuant to which he serves as our President & Chief Executive Officer. The employment agreement has an indefinite term. Dr. Cobuzzi is currently entitled to an initial annual base salary of $410,000, subject to increase at the discretion of the Board. Dr. Cobuzzi has the opportunity to earn a target annual bonus of 50 percent of his base salary. The Board may, in its discretion, pay a portion of Dr. Cobuzzi' 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. Cobuzzi' entire base salary and annual bonus will be paid in cash. For 2021, Dr. Cobuzzi' entire pro-rated 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).

William K. Hornung, Chief Financial Officer

Effective September 21, 2018, we entered into an amended and restated employment agreement with Mr. Hornung pursuant to which he serves as our Chief Financial Officer. The employment agreement has an indefinite term. Mr. Hornung was entitled to an annual base salary of $298,100 during 2020, 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 2021, Mr. Hornung'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).

Christopher D. Galloway, Chief Medical Officer

Effective October 19, 2020, we entered into an employment agreement with Dr. Galloway pursuant to which he serves as our Chief Medical Officer. The employment agreement has an indefinite term. Dr. Galloway is entitled to an initial annual base salary of $375,000, subject to increase at the discretion of the Board. Dr. Galloway has the opportunity to earn a target annual bonus of 40 percent of his base salary. 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 (applicable during employment and for 12 months thereafter) and non-solicitation provisions (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).

William R. Elder, General Counsel & Corporate Secretary

Effective September 23, 2020, we entered into an employment agreement with Mr. Elder pursuant to which he serves as our General Counsel & Corporate Secretary. The employment agreement has an indefinite term. Mr. Elder is entitled to an initial annual base salary of $250,000, subject to increase at the discretion of the Board. Mr. Elder has the opportunity to earn a target annual bonus of 30 percent of his base salary. The Board may, in its discretion, pay a portion of Mr. Elder'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. Elder's entire base salary and annual bonus will be paid in cash. For 2021, Mr. Elder's entire pro-rated 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).

Long-Term Equity Incentive Compensation and Other Compensatory Arrangements

The Compensation Committee administers the 2015 Equity Plan in which our named executive officers participate, the bonus payments made to our named executive officers provided for in the employment agreements described under the heading "—Employment Agreements," and any other compensation-related matters as they otherwise determine in their discretion. The option grants made for service during 2020 to the named executive officers vest and become exercisable in equal (or as near equal as possible) installments over a 36-month period until fully vested, subject to their continued employment through the applicable vesting date.

During 2021, the Compensation Committee determined that 50% of any annual long-term equity incentive awards granted to our named executive officers for service during the year would be granted at the outset of the year in the form of performance-based options the vesting of which will be dependent on the achievement of specified performance metrics during the year of grant. The remaining 50 percent were granted in the form of option awards subject to time-based vesting early in the subsequent year (i.e. 2022) at the discretion of the Compensation Committee in accordance with past practice. In 2022, the Compensation Committee determined to return to the Company's historic practice of granting all such awards as options subject to time-based vesting.

2021 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, capital raising transactions, and stock price performance.

Outstanding Equity Awards at Fiscal Year End

Option Awards

The table below provides information regarding unexercised stock option awards held by each of our named executive officers that remained outstanding as of December 31, 2021. Unless otherwise indicated, each grant was awarded under our 2015 Equity Plan.

Name	Award Type	Grant Date	Shares Underlying Unexercisable Options Exercisable	Shares Underlying Unexercisable Options Unexercisable	Exercise Price	Expiration Date
Robert J. Cobuzzi, Jr., Ph.D.	NQO	1/7/2020	118,600	—	$ 0.51	1/7/2030
	NQO	6/17/2020	61,300	—	$ 1.00	6/17/2030
	NQO	9/8/2020	197,917	277,083	$ 0.79	9/8/2030
	NQO	3/1/2021	14,920	38,793	$ 1.11	3/1/2031
	NQO**	3/1/2021	17,904	35,809	$ 1.11	3/1/2031
William K. Hornung	NQO	1/2/2018	6,000	—	$ 17.70	1/2/2028
	NQO	1/2/2019	16,334	—	$ 2.10	1/2/2029
	NQO	1/2/2020	35,067	17,533	$ 0.46	1/2/2030
	NQO	3/1/2021	34,103	88,668	$ 1.11	3/1/2031
	NQO**	3/1/2021	8,897	17,793	$ 1.11	3/1/2031
Christopher D. Galloway, M.D.	NQO*	10/19/2020	77,778	122,222	$ 0.85	10/19/2030
	NQO	3/1/2021	7,550	19,630	$ 1.11	3/1/2031
	NQO**	3/1/2021	9,060	18,119	$ 1.11	3/1/2031
William R. Elder	NQO*	9/22/2020	29,167	40,833	$ 0.82	9/22/2030
	NQO	3/1/2021	24,357	63,327	$ 1.11	3/1/2031
	NQO**	3/1/2021	6,947	13,894	$ 1.11	3/1/2031

* - Non-plan based equity award grant made as an inducement to the individual's acceptance of employment with the Company in accordance with Nasdaq Listing Rule 5635(c)(4).

** - Pursuant to the terms of the corresponding award agreements, two-thirds of the underlying shares originally granted were automatically forfeited due to the first patient in the ILD-DLCO Trial not being dosed on or before September 30, 2021. The Company announced dosing of the first patients in the ILD-DLCO Trial on December 16, 2021.

Restricted Stock Unit Awards

The table below provides information regarding restricted stock unit awards held by each of our named executive officers that remained outstanding as of December 31, 2021, if any. Each grant was awarded under our 2015 Equity Plan.

Name	Award Type	Grant Date	Number of Shares That Have Not Vested	Market Value of Shares That Have Not Vested*
Robert J. Cobuzzi, Jr., Ph.D.	RSU	1/7/2020	81,750	$ 25,343

* - Based on a price per share of $0.31, the closing price of our common stock on December 31, 2021 as reported by Nasdaq. The award was granted to Dr. Cobuzzi in connection with his appointment as a non-employee director in January 2020 and vests in six tri-monthly installments. The first such installment vested on October 31, 2021.

401(k) Retirement Plan

We maintain our 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 2021 and 2020 are reported in the "All Other Compensation" column of the Summary Compensation Table above.

Post-Termination Severance and Change in Control Arrangements

As described under the heading "—Employment Agreements," we have entered into employment agreements with each of Drs. Cobuzzi and Galloway and Messrs. Hornung and Elder 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 Dr. Cobuzzi's employment agreement, if his employment is terminated by us other than for "cause," death or "disability," or by Dr. Cobuzzi for "good reason" (as such terms are defined in the employment agreement), Dr. Cobuzzi 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 Dr. Cobuzzi will be entitled to receive the same severance benefits as described 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 Dr. Cobuzzi's employment is terminated by us without cause or by Dr. Cobuzzi for good reason, in either case, upon or within 24 months following a change of control, then Dr. Cobuzzi 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 each of Dr. Galloway and Messrs. Hornung and Elder, in the event that his 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 applicable 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 he will be entitled to receive the same severance benefits as described 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 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 in installments over 9 or 12 months in other cases). In addition, if the applicable executive's employment is terminated by the Company without cause or by the applicable executive for good reason, in either case, upon or within 24 months following a change of control, then the applicable executive 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 each of our current named executive officers, 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 named executives officers, upon a completion of a "change of control" (as defined in the 2015 Equity Plan), options held by our named executive officers 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.

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

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 1, 2022 for (i) each person or group of affiliated persons known by us to be the beneficial owner of more than 5% of our common stock, if any, (ii) each of our current directors; (iii) each of our current executive officers (as defined in Item 402(a)(3) of Regulation S-K under the Exchange Act); and (iv) all of our current directors and named executive officers as a group. As of March 1, 2022, to our knowledge, 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 shares of preferred stock, stock options or warrants that are exercisable or convertible within 60 days of March 1, 2022 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 and public documents filed with the SEC, including Forms 3 and 4, Schedules 13D and 13G and certain other documents, which information may not be accurate as of the Record Date.

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., 300 East Main Street, Suite 201, Charlottesville, Virginia 22902.

Name and Address of Beneficial Owner	Shares of Common Stock Beneficially Owned (1)	Common Stock Beneficial Ownership Percentage (2)
Current Directors		
Robert Adams (3)	166,515	0.2%
Robert J. Cobuzzi, Jr., Ph.D. (4)	551,507	0.5%
Eric Francois (5)	104,125	0.1%
Mark T. Giles (6)	210,173	0.2%
Jane H. Hollingsworth (7)	162,661	0.2%
Diana Lanchoney, M.D. (8)	104,125	0.1%
Alan Levin (9)	156,158	0.2%
Current Named Executive Officers		
William R. Elder (10)	115,827	0.1%
Christopher D. Galloway, M.D. (11)	171,063	0.2%
William K. Hornung (12)	142,717	0.1%
All Current Directors, Director Nominees, and Named Executive Officers as a Group (ten persons) (13)	**1,884,871**	**1.8%**

* Indicates less than 0.1%

1. Includes shares of common stock held as of March 1, 2022 plus shares of common stock that may be acquired upon exercise of options, warrants and other rights exercisable within 60 days of the March 1, 2022.
2. Based on 101,924,581 shares of common stock issued and outstanding as of March 1, 2022. 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 preferred stock, options, warrants and convertible securities exercisable or convertible within 60 days of March 1, 2022 held by such person and (ii) the non-exercise and non-conversion of all outstanding preferred stock, warrants, options and convertible securities held by all other persons (including our other directors and executive officers).
3. Consists of (a) 1,706 shares held directly by Mr. Adams, (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) 162,918 shares of common stock issuable upon the exercise of options exercisable within 60 days of March 1, 2022.
4. Consists of (a) 34,602 shares held directly by Dr. Cobuzzi and (b) 516,905 shares of common stock issuable upon the exercise of options exercisable within 60 days of March 1, 2022.
5. Consists of 104,125 shares of common stock issuable upon the exercise of options exercisable within 60 days of March 1, 2022.
6. 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) 156,366 shares of common stock issuable upon the exercise of options exercisable within 60 days of March 1, 2022. 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.
7. Consists of (a) 32,876 shares held directly by Ms. Hollingsworth and (b) 129,875 shares of common stock issuable upon the exercise of options exercisable within 60 days of March 1, 2022.
8. Consists of 104,125 shares of common stock issuable upon the exercise of options exercisable within 60 days of March 1, 2022.
9. Consists of (a) 1,654 shares held by Mr. Levin directly and (b) 154,504 shares of common stock issuable upon the exercise of options exercisable within 60 days of March 1, 2022.
10. Consists of (a) 15,000 shares held directly by Mr. Elder and (b) 100,827 shares of common stock issuable upon the exercise of options exercisable within 60 days of March 1, 2022.
11. Consists of (a) 20,000 shares held for the benefit of Dr. Galloway in his individual retirement account, (b) 10,000 shares held for the benefit of Dr. Galloway's wife in her individual retirement account, and (c) 141,063 shares of common stock issuable upon the exercise of options exercisable within 60 days of March 1, 2022.
12. Consists of 142,717 shares of common stock issuable upon the exercise of options exercisable within 60 days of March 1, 2022.
13. Includes 1,713,425 shares of common stock issuable upon the exercise of options exercisable within 60 days of March 1, 2022.

Delinquent Section 16(a) Reports

Section 16(a) of the Exchange Act 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, 2021, 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, 2021, except for the following, each of which were not timely filed: Forms 3 relating to Mr. Francois' and Dr. Lanchoney's respective elections to the Board on June 25, 2021, each filed on October 15, 2021; and a Form 4 relating to a July 1, 2021 grant of options and restricted stock units to Dr. Lanchoney in connection with her election to and service on the Board, filed on October 15, 2021.

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

Certain Relationships and Related Party Transactions

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 Capital 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, 2020 there has been no transaction 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. Furthermore, no family relationships exist among any of our directors or executive officers.

Director Independence

The information required by Item 13 of Form 10-K with respect to director independence included above under the heading, "Item 10. Directors, Executive Officers and Corporate Governance — Corporate Governance," is incorporated herein by reference.

ITEM 14. PRINCIPAL ACCOUNTING FEES AND SERVICES

Independent Registered Public Accounting Firm

The Audit Committee selected KPMG LLP as our independent registered public accounting firm for the fiscal year ending December 31, 2021. The Audit Committee's selection of KPMG LLP was ratified by our stockholders at our 2021 annual meeting of stockholders.

Independent Registered Public Accounting Firm's Fees

The table below presents fees billed to us for professional services rendered by KPMG LLP for the years ended December 31, 2021 and December 31, 2020.

	Aggregate Amount Billed	
	2021	2020
Audit Fees	$ 365,000	$ 508,060
Audit-Related Fees	$ —	$ —
Tax Fees	$ —	$ 80,000
All Other Fees	$ —	$ —
Total	$ 365,000	$ 588,060

Tax fees billed in 2020 represent fees paid to KPMG LLP in connection with an analysis under Section 382 of the Tax Code.

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 2021 and 2020 were permissible under applicable laws and regulations and were approved in advance by the Audit Committee in accordance with the rules adopted by the SEC in order to implement requirements of SOX.

PART IV

ITEM 15. EXHIBITS, FINANCIAL STATEMENT SCHEDULES

1. Our financial statements are included in Part II, Item 8 of this Annual Report.

2. All financial statement schedules have been omitted from this Item 15 as the required information is not applicable, is not present in amounts sufficient to require submission of such schedules, or because the information required is included in our financial statements or the related notes included in Part II, Item 8 of this Annual Report.

3. The exhibits set forth in the following "Index to Exhibits" are filed with, furnished with, and/or incorporated by reference into this Annual Report, as set forth therein. A copy of any of such exhibit 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., 300 East Main Street, Suite 201, Charlottesville, Virginia 22902, Attention: General Counsel.

INDEX TO EXHIBITS

Exhibit No.	Description	Method of Filing
3.1	Certificate of Incorporation of Diffusion Pharmaceuticals Inc., as amended	Incorporated by reference to Exhibit 3.1 to the registrant's annual report on Form 10-K for the year ended December 31, 2019
3.2	Bylaws of Diffusion Pharmaceuticals Inc., as amended	Incorporated by reference to Exhibit 3.4 to the registrant's annual report on Form 10-K for the year ended December 31, 2015
4.1	Form of 2017 Private Placement Warrant	Incorporated by reference to Exhibit 4.1 to the registrant's current report on Form 8-K filed on March 15, 2017
4.2	Form of 2018 Common Stock Warrant	Incorporated by reference to Exhibit 4.1 to the registrant's current report on Form 8-K filed on January 19, 2018
4.3	Form of 2018 Underwriter's Warrant	Incorporated by reference to Exhibit 4.2 to the registrant's current report on Form 8-K filed on January 22, 2018
4.4	Form of May 2019 Common Stock Warrant	Incorporated by reference to Exhibit 4.1 to the registrant's current report on Form 8-K filed on May 28, 2019
4.5	Form of May 2019 Placement Agent's Warrant	Incorporated by reference to Exhibit 4.2 to the registrant's current report on Form 8-K filed on May 28, 2019
4.6	Form of November 2019 Series I Common Stock Warrant	Incorporated by reference to Exhibit 4.1 to the registrant's current report on Form 8-K filed on November 13, 2019
4.7	Form of November 2019 Series II Common Stock Warrant	Incorporated by reference to Exhibit 4.2 to the registrant's current report on Form 8-K filed on November 13, 2019
4.8	Form of November 2019 Pre-Funded Common Stock Warrant	Incorporated by reference to Exhibit 4.3 to the registrant's current report on Form 8-K filed on November 13, 2019
4.9	Form of November 2019 Placement Agent's Warrant	Incorporated by reference to Exhibit 4.4 to the registrant's current report on Form 8-K filed on November 13, 2019
4.10	Form of December 2019 Common Stock Warrant	Incorporated by reference to Exhibit 4.1 to the registrant's current report on Form 8-K filed on December 13, 2019
4.11	Form of December 2019 Placement Agent's Warrant	Incorporated by reference to Exhibit 4.2 to the registrant's current report on Form 8-K filed on December 13, 2019
4.12	Form of May 2020 Common Stock Warrant	Incorporated by reference to Exhibit 4.1 to the registrant's current report on Form 8-K filed on May 8, 2020
4.13	Form of May 2020 Placement Agent's Warrant (In Respect of Exercise Transaction)	Incorporated by reference to Exhibit 4.2 to the registrant's current report on Form 8-K filed on May 8, 2020
4.14	Form of May 2020 Placement Agent's Warrant (In Respect of Offering Transaction)	Incorporated by reference to Exhibit 4.3 to the registrant's current report on Form 8-K filed on May 20, 2020
4.15	Form of February 2021 Underwriter's Warrant	Incorporated by reference to Exhibit 4.1 to the registrant's current report on Form 8-K filed on February 18, 2021
4.16	Description of Securities	Incorporated by reference to Exhibit 4.12 to the registrant's annual report on 10-K for the year ended December 31, 2019

10.1	Employment Agreement dated as of September 8, 2020 by and between Robert J. Cobuzzi, Jr., Ph.D. and Diffusion Pharmaceuticals Inc.*	Incorporated by reference to Exhibit 10.2 to the registrant's current report on Form 8-K filed on September 9, 2020
10.2	Amended and Restated Employment Agreement, dated as of September 21, 2018, by and between William Karl Hornung and Diffusion Pharmaceuticals Inc. *	Incorporated by reference to Exhibit 10.2 to the registrant's Current Report on Form 8-K filed September 27, 2018
10.3	Employment Agreement, dated as of October 19, 2020, by and between Christopher D. Galloway, M.D. and Diffusion Pharmaceuticals Inc. *	Incorporated by reference to Exhibit 10.1 to the registrant's Current Report on Form 8-K filed October 20, 2020
10.4	Employment Agreement, dated as of September 23, 2020, by and between William Elder and Diffusion Pharmaceuticals Inc. *	Incorporated by reference to Exhibit 10.1 to the registrant's Current Report on Form 8-K filed September 25, 2020
10.5	Diffusion Pharmaceuticals Inc. 2015 Equity Incentive Plan*	Incorporated by reference to Appendix C to the registrants definitive proxy statement on Schedule 14A filed on June 10, 2016
10.6	Amendment No. 1 to Diffusion Pharmaceuticals Inc. 2015 Equity Incentive Plan*	Incorporated by reference to Appendix B to the registrants definitive proxy statement on Schedule 14A filed on June 10, 2016
10.7	Form of Stock Option Award Agreement under 2015 Equity Incentive Plan*	Filed herewith
10.8	Form of Director RSU Agreement under 2015 Equity Incentive Plan*	Filed herewith
10.9	Form of Diffusion Pharmaceuticals LLC Stock Option Award Agreement*	Incorporated by reference to Exhibit 10.24 to the registrant's annual report on Form 10-K for the year ended December 31, 2015
10.10	Form of Indemnification Agreement between Diffusion Pharmaceuticals Inc. and each of its Directors and Officers*	Incorporated by reference to Exhibit 10.3 to the registrant's annual report on Form 10-K for the year ended December 31, 2015
21.1	Subsidiaries of Diffusion Pharmaceuticals Inc.	Filed herewith
23.1	Consent of KPMG LLP, independent registered public accounting firm	Filed herewith
31.1	Certification of Chief Executive Officer Pursuant to Section 302 of the Sarbanes-Oxley Act of 2002 and SEC Rule 13a-14(a)	Filed herewith
31.2	Certification of Principal Financial Officer Pursuant to Section 302 of the Sarbanes-Oxley Act of 2002 and SEC Rule 13a-14(a)	Filed herewith
32.1	Certification of Chief Executive Officer Pursuant to 18 U.S.C. Section 1350, as Adopted Pursuant to Section 906 of the Sarbanes-Oxley Act of 2002	Filed herewith
101	The following materials from the registrant's annual report on Form 10-K for the year ended December 31, 2021, formatted in iXBRL (Inline 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
104	Cover Page Interactive Data File (embedded within the Inline XBRL and contained in Exhibit 101)	
*	Indicates 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 18, 2022

DIFFUSION PHARMACEUTICALS INC.
By: /s/ Robert J. Cobuzzi, Jr., Ph.D.
Robert J. Cobuzzi, Jr., Ph.D.
President, Chief Executive Officer, and Director
(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.

Name and Signature	Title	Date
/s/ Robert J. Cobuzzi, Jr., Ph.D. Robert J. Cobuzzi, Jr., Ph.D.	President, Chief Executive Officer, and Director (Principal Executive Officer)	March 18, 2022
/s/ William K. Hornung William K. Hornung	Chief Financial Officer (Principal Financial and Accounting Officer)	March 18, 2022
/s/ Jane H. Hollingsworth Jane H. Hollingsworth	Chair of the Board	March 18, 2022
/s/ Robert Adams Robert Adams	Director	March 18, 2022
/s/ Eric Francois Eric Francois	Director	March 18, 2022
/s/ Mark T. Giles Mark T. Giles	Director	March 18, 2022
/s/ Diana Lanchoney Diana Lanchoney	Director	March 18, 2022
/s/ Alan Levin Alan Levin	Director	March 18, 2022

Diffusio$_2$n
Pharmaceuticals Inc.

STOCK OPTION AGREEMENT

This STOCK OPTION AGREEMENT (this "***Agreement*")** is entered into and effective as of [_____], 202[__] (the "***Grant Date***") by and between Diffusion Pharmaceuticals Inc., a Delaware corporation (the "***Company***"), and [_____] ("***Optionee***").

A. The Company has adopted the Diffusion Pharmaceuticals Inc. 2015 Equity Incentive Plan (as such plan may be amended from time to time, the "***Plan***") authorizing the Board of Directors (the "***Board***") of the Company, or a committee as provided for in the Plan (the Board or such a committee to be referred to as the "***Committee***"), to grant stock options, among other incentive awards, to certain individuals.

B. The Company desires to grant [an incentive/a non-qualified] stock option to purchase shares of common stock, par value $0.001 per share, of the Company (the "***Common Stock***") to Optionee pursuant to the Plan.

C. All of the capitalized terms used in this Agreement not otherwise defined in this Agreement have the same respective meanings as defined in the Plan.

NOW, THEREFORE, in consideration of the mutual promises and covenants hereinafter set forth, the Company and Optionee agree as follows:

1. Grant of Option; Exercise Price. The Company hereby grants to Optionee, upon the terms and subject to the conditions set forth in this Agreement and the Plan, and effective as of the Grant Date, an option (the "***Option***") to purchase all or any portion of [_____] shares (the "***Option Shares***") of the Company's Common Stock, at an exercise price of $[_____] per share, which represents 100% of the Fair Market Value of a share of Common Stock on the Grant Date, as determined in accordance with the Plan (such exercise price, as adjusted from time to time pursuant to Section 5 of this Agreement and Section 4.3 of the Plan, the "***Exercise Price***"). The Option [is/is not] intended to be an "incentive stock option," as that term is used in Section 422 of the Internal Revenue Code of 1986, as amended (the "***Code***").

2. Vesting. The option will vest and become exercisable in 36 equal (or as nearly equal as possible) installments on the last calendar day of each month over a 36-month period beginning on [_____].

3. Exercise of Option.

3.1. Notice; Payment. Subject to the terms and conditions set forth in this Agreement, including vesting of the Option in Section 2 of this Agreement and termination of the Option in Section 4 of this Agreement, and the Plan, the Option may be exercised, in whole or in part, at any time and from time to time, by delivery to the Company of written notice of the exercise of the Option, in substantially the form as provided by the Company, stating the number of Option Shares being purchased (the "***Purchased Shares***"), and accompanied by payment in full of the total aggregate Exercise Price of the Purchased Shares. The Exercise Price shall be payable in full in any one of the following alternative forms:

a) Full payment in cash, personal check or certified bank or cashier's check;

b) Any broker assisted cashless exercise procedure which is acceptable to the Company;

c) Cashless net exercise.

$X = Y - [(A)(YB)]$

Where: X = the number of shares of Common Stock to be issued to Optionee.

Y = the number of Purchased Shares.

A = the Exercise Price.

B = the Fair Market Value of one share of Common Stock on the date of exercise.

3.2. Issuance of Purchased Shares; No Fractional Shares. Following receipt of the exercise notice and the payment referred to above (or upon a cashless net exercise), Optionee shall receive the number of shares of Common Stock equal to a number (as determined below) of shares of Common Stock computed using the following formula: and the payment referred to above, the Company shall, as soon as reasonably practicable thereafter, cause certificates (or book-entry notations) representing the Purchased Shares (or such fewer number of Purchased Shares if a cashless net exercise is used) to be delivered to Optionee either at Optionee's address set forth in the records of the Company or at such other address as Optionee may designate in writing to the Company or issue and deposit the Purchased Shares for Optionee's benefit with any broker with which Optionee has an account relationship or the Company has engaged to provide such services under the Plan; provided, however, that the Company shall not be obligated to issue a fraction or fractions of a share otherwise issuable upon exercise of the Option, and may pay to Optionee, in cash or cash equivalent, the Fair Market Value of any such fraction or fractions of a share as of the date of exercise. If requested by the Company in connection with any exercise of the Option, Optionee shall also deliver this Agreement to the Company, which shall endorse hereon a notation of the exercise and, and if the Option is exercised in part, shall return this Agreement to Optionee. The date of exercise of an Option that is validly exercised shall be deemed to be the date on which there shall have been delivered to the Company the notice referred to in Section 3.1 of this Agreement and full payment of the Exercise Price of the Purchased Shares. Optionee shall not be deemed to be a holder of any Purchased Shares pursuant to exercise of the Option until the date of issuance of a stock certificate or book-entry notation to Optionee for such shares following payment in full for the Purchased Shares.

3.3. Tax Withholding. The Company is entitled to (a) withhold and deduct from future wages of Optionee (or from other amounts that may be due and owing to Optionee from the Company or a Subsidiary), or make other arrangements for the collection of, all amounts the Company reasonably determines are necessary to satisfy any and all federal, foreign, state and local withholding and employment related tax requirements attributable to the Option, including, without limitation, the grant, exercise or vesting of, the Option; (b) withhold cash paid or payable or shares of Common Stock from the shares issued or otherwise issuable to Optionee in connection with the Option; or (c) require Optionee promptly to remit the amount of such withholding to the Company before taking any action, including issuing any shares of Common Stock, with respect to the Option. Shares of Common Stock issued or otherwise issuable to Optionee in connection with the Option that gives rise to the tax withholding obligation that are withheld for purposes of satisfying Optionee's withholding or employment-related tax obligation will be valued at their Fair Market Value on the Tax Date.

3.4. Remaining Option Shares. Option Shares will no longer be outstanding under the Option (and will therefore not thereafter be exercisable) following the exercise of the Option to the extent of (a) shares used to pay the Exercise Price of an Option under the "cashless net exercise" method (b) shares actually delivered to Optionee as a result of such exercise and (c) any shares withheld for purposes of tax withholding.

4. Termination of Option.

4.1. Time of Termination. Except as provided in this Section 4 and Section 5 of this Agreement, the Option shall terminate, no longer be exercisable and expire at 5:00 p.m., Eastern Time, on [_____] (the "***Time of Termination***").

4.2. Termination for Cause. In the event Optionee's employment (in the event that Optionee is an Employee) or other service (in the event that Optionee is a Consultant) with the Company and all Subsidiaries is terminated by the Company for Cause, the Option will immediately terminate without notice of any kind, and the Option will no longer be exercisable.

4.3. Termination Due to Death, Disability or Retirement . In the event Optionee's employment (in the event that Optionee is an Employee) or other service (in the event that Optionee is a Consultant) with the Company and all Subsidiaries is terminated by reason of Optionee's death, Disability or Retirement, the Option will remain exercisable, to the extent exercisable as of the date of such termination, for a period of one (1) year after such termination (but in no event after the Time of Termination).

4.4. Termination for Other Reasons. In the event Optionee's employment (in the event that Optionee is an Employee) or other service (in the event that Optionee is a Consultant) with the Company and all Subsidiaries is terminated for any other reason, the Option will, to the extent exercisable as of such termination, remain exercisable for a period of three (3) months after such termination (but in no event after the Time of Termination).

4.5. Effect of Actions Constituting Cause or Adverse Action. Notwithstanding anything in this Agreement to the contrary and in addition to the rights of the Committee under Sections 13.5 and 13.6 of the Plan, if Optionee is determined by the Committee, acting in its sole discretion, to have taken any action that would constitute Cause or an Adverse Action during or after the termination of employment or other service with the Company or a Subsidiary, irrespective of whether such action or the Committee's determination occurs before or after termination of Optionee's employment or other service with the Company or any Subsidiary and irrespective of whether or not Optionee was terminated as a result of such Cause or Adverse Action, (a) all rights of Optionee under the Option and this Agreement will terminate and be forfeited without notice of any kind, and (b) the Committee in its sole discretion will have the authority to rescind the exercise, vesting, settlement or issuance of, or payment in respect of, the Option that was exercised, vested, settled or issued, or as to which such payment was made, and to require Optionee to pay to the Company, within ten (10) days of receipt from the Company of notice of such rescission, any amount received or the amount of any gain realized as a result of such rescinded exercise, vesting, settlement, issuance or payment (including any dividends paid or other distributions made with respect to any shares of Common Stock subject to the Option). The Company may defer the exercise of the Option for a period of up to six (6) months after receipt of Optionee's written notice of exercise or the issuance of Purchased Shares upon the vesting of the Option for a period of up to six (6) months after the date of such vesting in order for the Committee to make any determination as to the existence of Cause or an Adverse Action. The Company will be entitled to withhold and deduct from future wages of Optionee (or from other amounts that may be due and owing to Optionee from the Company or a Subsidiary) or make other arrangements for the collection of all amounts necessary to satisfy such payment obligations. This Section 4.5 will not apply to the Option following a Change in Control.

4.6. Clawback/Forfeiture. The Option and Option Shares issued or issuable pursuant to the Option are subject to forfeiture or clawback by the Company to the extent required and allowed by law, including the Dodd-Frank Wall Street Reform and Consumer Protection Act of 2010 and the Sarbanes Oxley Act of 2002 and any implementing rules and regulations promulgated thereunder, and pursuant to any forfeiture, clawback or similar policy of the Company, as such laws, rules, regulations and policy may be in effect from time to time.

5. Adjustments. In the event of any reorganization, merger, consolidation, recapitalization, liquidation, reclassification, stock dividend, stock split, combination of shares, rights offering, divestiture, or extraordinary dividend (including a spin-off), or any other similar change in the corporate structure or shares of the Company, the Committee (or, if the Company is not the surviving corporation in any such transaction, the board of directors of the surviving corporation), will make appropriate adjustment (which determination will be conclusive) as to the number and kind of securities or other property (including cash) subject to, and the Exercise Price of, the Option in order to prevent dilution or enlargement of the rights of Optionee.

6. Change in Control. The Option shall become immediately vested and exercisable upon completion of a Change in Control and remain exercisable through the Time of Termination regardless of whether Optionee remains in the employment or service of the Company. Notwithstanding any of the foregoing, in connection with a Change in Control, the Committee, in its sole discretion, at any time after the grant of the Option, may take whatever action it deems appropriate pursuant to Section 15.3 of the Plan.

7. Rights as a Stockholder. Optionee will have no rights as a stockholder of the Company unless and until all conditions to the effective exercise of the Option (including, without limitation, the conditions set forth in Section 3 of this Agreement) have been satisfied and Optionee has become the holder of record of such shares. No adjustment will be made for dividends or distributions with respect to the Option as to which there is a record date preceding the date Optionee becomes the holder of record of such shares, except as may otherwise be provided in the Plan or determined by the Committee in its sole discretion.

8. Restrictions on Transfer. Except pursuant to testamentary will or the laws of descent and distribution or as otherwise expressly permitted by the Plan, no right or interest of Optionee in the Option prior to exercise may be assigned or transferred, or subjected to any lien, during the lifetime of Optionee, either voluntarily or involuntarily, directly or indirectly, by operation of law or otherwise. Optionee, however, will be entitled to designate a beneficiary to receive the Option upon Optionee's death, and, in the event of Optionee's death, exercise of the Option (to the extent permitted pursuant to Sections 2 and 4 of this Agreement) may be made by Optionee's legal representatives, heirs and legatees.

9. Market Stand-off. Optionee, if so requested by the Company or any representative of the underwriters in connection with a firmly underwritten public offering of securities by the Company pursuant to a registration statement under the Securities Act following the date of this Agreement, shall not sell or otherwise transfer any Option Shares during the 180-day period following the effective date of such registration statement. The Company may impose stop-transfer instructions with respect to securities subject to the foregoing restriction until the end of such 180-day period. This Section 9 will not apply to the sale of any Option Shares to an underwriter pursuant to an underwriting agreement and shall only be applicable to Optionee if all then current executive officers and directors of the Company enter into similar agreements.

10. Employment or Service. Nothing in this Agreement or the Plan will interfere with or limit in any way the right of the Company or any Subsidiary to terminate the employment or service of Optionee at any time, nor confer upon Optionee any right to continue in the employment or other service with the Company or any Subsidiary.

11. Option Subject to Plan. The Option and the Option Shares granted and issued pursuant to this Agreement have been granted and issued under, and are subject to the terms of, the Plan. The terms of the Plan are incorporated by reference in this Agreement in their entirety, and Optionee, by execution of this Agreement, acknowledges having received a copy of the Plan. The provisions of this Agreement will be interpreted as to be consistent with the Plan, and any ambiguities in this Agreement will be interpreted by reference to the Plan. In the event that any provision of this Agreement is inconsistent with the terms of the Plan, the terms of the Plan will prevail. All of the capitalized terms used in this Agreement not otherwise defined in this Agreement have the same respective meanings as defined in the Plan.

12. General Provisions.

12.1. Governing Law; Venue. This Agreement and all rights and obligations under this Agreement will be governed by and construed exclusively in accordance with the laws of the State of Delaware, notwithstanding the conflicts of laws principles of any jurisdictions. By acceptance of the Option, Optionee is deemed to submit to the exclusive jurisdiction and venue of the federal or state courts of the State of Illinois to resolve any and all issues that may arise out of or relate to the Option or this Agreement.

12.2. Entire Agreement. This Agreement and the Plan set forth the entire agreement and understanding of the parties to this Agreement with respect to the grant and exercise of the Option and the administration of the Plan and supersede all prior agreements, arrangements, plans, and understandings relating to the grant and exercise of the Option and the administration of the Plan.

12.3. Failure to Enforce Not a Waiver. The failure of the Company or Optionee to enforce at any time any provision of this Agreement shall in no way be construed to be a waiver of such provision or of any other provision hereof.

12.4. Notices. All notices, requests, demands and other communications (collectively, "***Notices***") given pursuant to this Agreement shall be in writing, and shall be delivered by personal service, courier, facsimile transmission, email transmission of a pdf format data file or by United States first class, registered or certified mail, postage prepaid, addressed to the party at the address set forth on the signature page of this Agreement. Any Notice, other than a Notice sent by registered or certified mail, shall be effective when received; a Notice sent by registered or certified mail, postage prepaid return receipt requested, shall be effective on the earlier of when received or the third day following deposit in the United States mails. Any party may from time to time change its address for further Notices hereunder by giving notice to the other party in the manner prescribed in this Section 12.4.

12.5. Successors and Assigns. Except to the extent specifically limited by the terms and provision of this Agreement, this Agreement shall be binding upon and inure to the benefit of the parties hereto and their respective successors, assigns, heirs, and personal representatives.

12.6. Execution. This Agreement may be executed in two or more counterparts, all of which when taken together shall be considered one and the same agreement and shall become effective when counterparts have been signed by each party and delivered to the other party, it being understood that both parties need not sign the same counterpart. In the event that any signature is delivered by facsimile transmission or by email delivery of a "pdf" format data file, such signature shall create a valid and binding obligation of the party executing (or on whose behalf such signature is executed) with the same force and effect as if such facsimile or "pdf" signature page were an original thereof.

12.7. Titles, Captions and Sections. Titles and captions contained in this Agreement are inserted for convenience of reference only and do not constitute a part of this Agreement for any other purpose. References to Sections in this Agreement refer to Sections of this Agreement unless otherwise stated.

12.8. Nature of the Grant. In accepting the Option and by execution of this Agreement, Optionee acknowledges that:

a) The Plan is established voluntarily by the Company, it is discretionary in nature and it may be modified, amended, suspended, or terminated by the Company in its sole discretion at any time, unless otherwise provided in the Plan.

b) The grant of the Option is voluntary and occasional and does not create any contractual or other right to receive future Option grants, or benefits in lieu of Option grants, even if Option grants have been granted repeatedly in the past.

c) All decisions with respect to future Option grants, if any, will be at the sole discretion of the Company.

d) Optionee is voluntarily participating in the Plan.

e) The Option grant is not part of normal or expected compensation or salary for any purposes, including, but not limited to, calculating any severance, resignation, termination, redundancy, end of service payments, bonuses, long-service awards, pension or retirement benefits or similar payments and in no event shall be considered as compensation for, or relating in any way to, past services for the Company.

f) In the event that Optionee is not an employee of the Company, the Option will not be interpreted to form an employment contract or relationship with the Company.

g) The future value of the Common Stock is unknown and cannot be predicted with certainty and if the Option vests and Optionee exercises the Option in accordance with the terms of this Agreement and is issued Purchased Shares, the value of those shares may increase or decrease.

h) In consideration of the grant of the Option, no claim or entitlement to compensation or damages shall arise from termination of the Option or diminution in value of the Option or Purchased Shares acquired upon exercise of the Option resulting from termination of Optionee's employment or service by the Company (for any reason whatsoever and whether or not in breach of local labor laws) and Optionee irrevocably releases the Company and its Subsidiaries, and their respective directors, officers, employees and agents, from any such claim that may arise; if, notwithstanding the foregoing, any such claim is found by a court of competent jurisdiction to have arisen, then, by acceptance of the Option and execution of this Agreement, Optionee shall be deemed irrevocably to have waived his or her entitlement to pursue such claim.

i) The Company is not providing any tax, legal or financial advice, nor is the Company making any recommendations regarding Optionee's participation in the Plan, or Optionee's purchase or sale of the underlying Option Shares.

j) Optionee is hereby advised to consult with his or her own personal tax, legal and financial advisors regarding his or her participation in the Plan before taking any action related to the Plan or the Option.

13. [Incentive Stock Option Limitations.

13.1 Limitation on Amount. To the extent that the aggregate Fair Market Value (determined as of the Grant Date) of the shares of Common Stock with respect to which incentive stock options (within the meaning of Section 422 of the Code) are exercisable for the first time by the Optionee during any calendar year (under the Plan and any other incentive stock option plans of the Company or any subsidiary or parent corporation of the Company (within the meaning of the Code)) exceeds $100,000 (or such other amount as may be prescribed by the Code from time to time), such excess incentive stock options will be treated as non-statutory stock options in the manner set forth in the Plan.

13.2 Limitation on Exercisability; Disposition of Option Shares. Any incentive stock option that remains unexercised more than one year following termination of employment by reason of death or disability or more than three months following termination for any reason other than death or disability will thereafter be deemed to be a non-statutory stock option. In addition, in the event that a disposition (as defined in Section 424(c) of the Code) of shares of Common Stock acquired pursuant to the exercise of an incentive stock option occurs prior to the expiration of two years after its date of grant or the expiration of one year after its date of exercise (a "disqualifying disposition"), such incentive stock option will, to the extent of such disqualifying disposition, be treated in a manner similar to a non-statutory stock option.

13.3. No Representation or Warranty. Section 422 of the Code and the rules and regulations thereunder are complex, and neither the Plan nor this Agreement purports to summarize or otherwise set forth all of the conditions that need to be satisfied in order for this Option to qualify as an incentive stock option. In addition, this Option may contain terms and conditions that allow for exercise of this Option beyond the periods permitted by Section 422 of the Code, including, without limitation, the periods described in Sections 2 and 4 of this Agreement. Accordingly, the Company makes no representation or warranty regarding whether the exercise of this Option will qualify as the exercise of an incentive stock option, and the Company recommends that the Optionee consult with the Optionee's own advisors before making any determination regarding the exercise of this Option or the sale of the Option Shares.]

[*Remainder of page intentionally left blank; Signature page follows*]

IN WITNESS WHEREOF, the parties to this Agreement have executed this Agreement effective as of the Grant Date.

OPTIONEE:

_____

Name: [_____]

DIFFUSION PHARMACEUTICALS INC.

_____

By: William Elder

Title: General Counsel

Address: 300 East Main Street, Suite 201

Charlottesville, VA 22902

By execution of this Agreement, Optionee acknowledges having received a copy of the Plan.

Diffusio$_2$n Pharmaceuticals Inc.

NON-EMPLOYEE DIRECTOR

RESTRICTED STOCK UNIT AGREEMENT

This RESTRICTED STOCK UNIT AGREEMENT (this "***Agreement*")** is made, entered into, and effective as of [____], 202[_] (the "***Grant Date***") by and between Diffusion Pharmaceuticals Inc., a Delaware corporation (the "***Company***"), and [____] ("***Director***").

A. The Company has adopted the Diffusion Pharmaceuticals Inc. 2015 Equity Incentive Plan (as such plan may be amended and/or restated from time to time, the "***Plan***") which authorizes the Board of Directors of the Company (the "***Board***"), or a committee thereof as provided for in the Plan (the Board or such committee in such capacity, the "***Committee***"), to grant restricted incentive awards to Participants, including Restricted Stock Units.

B. The Company desires to grant Restricted Stock Units denominated in shares of common stock, par value $0.001 per share, of the Company (the "***Common Stock***") to the Director pursuant to the Plan.

NOW, THEREFORE, in consideration of the mutual promises and covenants hereinafter set forth, the Company and Director agree as follows:

1. RSUs Subject to Plan; Defined Terms. The RSUs and the RSU Shares (each as defined in Section 2 below) granted and issued (if any) pursuant to this Agreement have been granted and issued under, and are subject to the terms of, the Plan. The terms of the Plan are incorporated by reference in this Agreement in their entirety, and Director, by execution of this Agreement, acknowledges having received a copy of the Plan. The provisions of this Agreement will be interpreted as to be consistent with the Plan, and any ambiguities in this Agreement will be interpreted by reference to the Plan. In the event any provision of this Agreement is inconsistent with the terms of the Plan, the terms of the Plan will prevail. All capitalized terms used and not otherwise defined in this Agreement have the meanings given to them in the Plan.

2. Grant of Restricted Stock Unit Award. The Company hereby grants [____] Restricted Stock Units (the "***RSUs***"), denominated in shares of Common Stock (the "***RSU Shares***"), to the Director as of the Grant Date stated above.

3. Vesting.

   a. Vesting. Subject to the provisions of this Section 3, the RSUs subject to this Award shall become vested on the dates set forth below, provided that the Director has not incurred a "Separation from Service" within the meaning of Section 409A(a)(2)(A)(i) of the Code and Treas. Reg. Section 1.409A-1(h), other than due to the Director's death or removal from the Board without cause, in which cases the RSUs shall become vested upon such event. There shall be no proportionate or partial vesting in the periods prior to the vesting date.

Dates	**# of Shares**

   b. Change in Control. The RSUs shall become immediately vested upon completion of a Change in Control. Notwithstanding any of the foregoing, in connection with a Change in Control, the Committee, in its sole discretion, at any time after the grant of the RSUs, may take whatever action it deems appropriate pursuant to Section 15.3 of the Plan.

   c. Forfeiture. Except as set forth in Section 3(a), all unvested RSUs shall be immediately forfeited upon the Director's termination of service with the Board.

   d. Clawback. The RSUs and RSU Shares issued or issuable pursuant to the RSUs are subject to forfeiture or clawback by the Company to the extent required and allowed by law, including the Dodd-Frank Wall Street Reform and Consumer Protection Act of 2010 and the Sarbanes Oxley Act of 2002 and any implementing rules and regulations promulgated thereunder, and pursuant to any forfeiture, clawback or similar policy of the Company, as such laws, rules, regulations and policy may be in effect from time to time.

4. Delivery of Shares. Subject to the provisions of Section 17 hereof, within sixty (60) days following the applicable vesting date of the RSUs (or as soon as practicable thereafter), the Director shall receive the number of shares of Common Stock that correspond to the number of RSUs that have become vested on the applicable vesting date, less a number of shares of Common Stock equal to the product of (i) the Fair Market Value of the shares of Common Stock on the Tax Date and (ii) the highest marginal Federal tax rate applicable to individuals, with the result rounded down to the nearest whole share (the "***Tax Reduction***"). The Fair Market Value of the shares of Common Stock subject to the Tax Reduction shall be paid to the Director in cash at the same time as the delivery of the shares of Common Stock pursuant to this Section 4 (collectively, the "***RSU Settlement***").

5. Rights as a Stockholder; Adjustments.

    a. Rights as a Stockholder. Director will have no rights as a stockholder of the Company unless and until all conditions to the effective settlement of the RSUs have been satisfied and Director has become the holder of record of such shares. No adjustment will be made for dividends or distributions with respect to the RSUs as to which there is a record date preceding the date Director becomes the holder of record of such shares, except as may otherwise be provided in the Plan or determined by the Committee in its sole discretion.

    b. Adjustments. In the event of any reorganization, merger, consolidation, recapitalization, liquidation, reclassification, stock dividend, stock split, combination of shares, rights offering, divestiture, or extraordinary dividend (including a spin-off), or any other similar change in the corporate structure or shares of the Company, the Committee (or, if the Company is not the surviving corporation in any such transaction, the board of directors of the surviving corporation), will make appropriate adjustment (which determination will be conclusive) as to the number and kind of securities or other property (including cash) subject to the RSUs in order to prevent dilution or enlargement of the rights of Director.

6. Restrictions on Transfer. Except pursuant to testamentary will or the laws of descent and distribution or as otherwise expressly permitted by the Plan, no right or interest of Director in the RSUs prior to exercise may be assigned or transferred, or subjected to any lien, during the lifetime of Director, either voluntarily or involuntarily, directly or indirectly, by operation of law or otherwise. Director, however, will be entitled to designate a beneficiary to receive the RSUs upon Director's death, and, in the event of Director's death, settlement of the RSUs (to the extent otherwise permitted hereby) may be made to Director's legal representatives, heirs and legatees.

7. Governing Law; Venue. This Agreement and all rights and obligations under this Agreement will be governed by and construed exclusively in accordance with the laws of the State of Delaware, notwithstanding the conflicts of laws principles of any jurisdictions. By acceptance of the RSUs, Director is deemed to submit to the exclusive jurisdiction and venue of the federal or state courts of the State of Illinois to resolve any and all issues that may arise out of or relate to the RSUs or this Agreement. The obligation of the Company to sell and deliver Common Stock hereunder is subject to applicable laws and to the approval of any governmental authority required in connection with the authorization, issuance, sale, or delivery of such Common Stock.

8. Tax Withholding. If the Director is subject to wage withholding at the source under the Code with respect to compensation paid to the Director by the Company, then the following provisions of this Section 8 shall apply: The Company may require the Director to pay to the Company, an amount the Company deems necessary to satisfy its current or future obligation to withhold federal, state or local income or other taxes, if any, that the Director incurs as a result of the Award. With respect to any required tax withholding, the Director may (a) direct the Company to withhold from the shares of Common Stock to be issued to the Director under this Agreement, an amount sufficient to satisfy any federal, state, local and foreign taxes of any kind which the Company, in its sole discretion, deems necessary to be withheld or remitted to comply with the Code and/or any other applicable law, rule or regulation with respect to the RSUs (such amount, in the aggregate, the "***Withholding Obligation***"), which determination will be based on the shares' Fair Market Value on the Tax Date; (b) deliver to the Company shares of Common Stock sufficient to satisfy the Withholding Obligation, based on the shares' Fair Market Value on the Tax Date; or (c) deliver cash to the Company sufficient to satisfy the Withholding Obligation. Without limiting the foregoing, the Company shall withhold shares of Common Stock otherwise deliverable to the Director hereunder in order to pay the Director's income and employment taxes due upon vesting of the RSUs, but only to the extent permitted by applicable accounting rules so as not to affect accounting treatment.

9. Market Stand-off. Director, if so requested by the Company or any representative of the underwriters in connection with a firmly underwritten public offering of securities by the Company pursuant to a registration statement under the Securities Act following the date of this Agreement, shall not sell or otherwise transfer any RSU Shares during the 180-day period following the effective date of such registration statement. The Company may impose stop-transfer instructions with respect to securities subject to the foregoing restriction until the end of such 180-day period. This Section 9 will not apply to the sale of any RSU Shares to an underwriter pursuant to an underwriting agreement and shall only be applicable to Director if all then current executive officers and directors of the Company enter into similar agreements.

10. Nature of the Grant. In accepting the RSUs and by execution of this Agreement, Director acknowledges that:

a. The Plan is established voluntarily by the Company, it is discretionary in nature and it may be modified, amended, suspended, or terminated by the Company in its sole discretion at any time, unless otherwise provided in the Plan.

b. The grant of the RSUs is voluntary and occasional and does not create any contractual or other right to receive future RSU grants, or benefits in lieu of RSU grants, even if RSU grants have been granted repeatedly in the past.

c. All decisions with respect to future RSU grants, if any, will be at the sole discretion of the Company.

d. Director is voluntarily participating in the Plan.

e. This grant of RSUs is not part of normal or expected compensation or salary for any purposes, including, but not limited to, calculating any severance, resignation, termination, redundancy, end of service payments, bonuses, long-service awards, pension or retirement benefits or similar payments and in no event shall be considered as compensation for, or relating in any way to, past services for the Company.

f. In the event that Director is not an employee of the Company, the RSUs will not be interpreted to form an employment contract or relationship with the Company.

g. The future value of the Common Stock is unknown and cannot be predicted with certainty and if the RSUs vest in accordance with the terms of this Agreement and RSU Shares are issued in settlement thereof, the value of those shares may increase or decrease.

h. In consideration of the grant of the RSUs, no claim or entitlement to compensation or damages shall arise from termination of the RSUs or diminution in value of the RSUs or RSU Shares resulting from termination of Director's employment or service by the Company (for any reason whatsoever and whether or not in breach of local labor laws) and Director irrevocably releases the Company and its Subsidiaries, and their respective directors, officers, employees and agents, from any such claim that may arise; if, notwithstanding the foregoing, any such claim is found by a court of competent jurisdiction to have arisen, then, by acceptance of the RSUs and execution of this Agreement, Director shall be deemed irrevocably to have waived his or her entitlement to pursue such claim.

i. The Company is not providing any tax, legal or financial advice, nor is the Company making any recommendations regarding Director's participation in the Plan, or Director's purchase or sale of the underlying RSU Shares.

j. Director is hereby advised to consult with his or her own personal tax, legal and financial advisors regarding his or her participation in the Plan before taking any action related to the Plan or the RSUs.

11. Entire Agreement. This Agreement and the Plan set forth the entire agreement and understanding of the parties to this Agreement with respect to the grant and settlement of the RSUs and the administration of the Plan and supersede all prior agreements, arrangements, plans, and understandings relating to the grant and settlement of the RSUs and the administration of the Plan. This Agreement may be amended by the Board or by the Committee at any time (a) if the Board or the Committee determines, in its sole discretion, that an amendment is necessary or advisable in light of any addition to or change in any federal or state, tax or securities law or other law or regulation, which change occurs after the Grant Date and by its terms applies to the Award; or (b) other than in the circumstances described in clause (a) or provided in the Plan, with the Director's consent.

12. Notices. All notices, requests, demands and other communications (collectively, "***Notices***") given pursuant to this Agreement shall be in writing, and shall be delivered by personal service, courier, facsimile transmission, email transmission of a pdf format data file or by United States first class, registered or certified mail, postage prepaid, addressed to the party at the address set forth on the signature page of this Agreement. Any Notice, other than a Notice sent by registered or certified mail, shall be effective when received; a Notice sent by registered or certified mail, postage prepaid return receipt requested, shall be effective on the earlier of when received or the third day following deposit in the United States mails. Any party may from time to time change its address for further Notices hereunder by giving notice to the other party in the manner prescribed in this Section 12.

13. Employment or Service. Nothing in this Agreement or the Plan will interfere with or limit in any way the right of the Company or any Subsidiary to terminate the employment or service of Director at any time, nor confer upon Director any right to continue in the employment or other service with the Company or any Subsidiary.

14. Transfer of Personal Data. The Director authorizes, agrees and unambiguously consents to the transmission by the Company (or any Subsidiary) of any personal data information related to the RSUs awarded under this Agreement for legitimate business purposes (including, without limitation, the administration of the Plan). This authorization and consent is freely given by the Director.

15. Compliance with Securities Laws. Notwithstanding any provision of this Agreement to the contrary, the issuance of the RSUs and any RSU Shares pursuant to this Agreement will be subject to compliance with all applicable requirements of federal, state, or foreign law with respect to such securities and with the requirements of any stock exchange or market system upon which the Common Stock may then be listed. No Common Stock will be issued hereunder if such issuance would constitute a violation of any applicable federal, state, or foreign securities laws or other law or regulations or the requirements of any stock exchange or market system upon which the Stock may then be listed. The inability of the Company to obtain from any regulatory body having jurisdiction the authority, if any, deemed by the Company's legal counsel to be necessary to the lawful issuance and sale of any shares subject to the Award will relieve the Company of any liability in respect of the failure to issue such shares of Common Stock as to which such requisite authority has not been obtained. As a condition to any issuance hereunder, the Company may require the Director to satisfy any qualifications that may be necessary or appropriate to evidence compliance with any applicable law or regulation and to make any representation or warranty with respect to such compliance as may be requested by the Company. From time to time, the Board and appropriate officers of the Company are authorized to take the actions necessary and appropriate to file required documents with governmental authorities, stock exchanges, and other appropriate Persons to make shares of Common Stock available for issuance.

16. Section 409A. This Agreement and the Plan are intended to comply with the applicable requirements of Section 409A of the Code and shall be limited, construed and interpreted in accordance with such intent. To the extent that this Award is subject to Section 409A of the Code, it shall be paid in a manner that will comply with Section 409A of the Code, including proposed, temporary or final regulations or any other guidance issued by the Secretary of the Treasury and the Internal Revenue Service with respect thereto. The Company shall have no liability to a Director, or any other party, if an Award that is intended to be exempt from, or compliant with, Section 409A of the Code is not so exempt or compliant or for any action taken by the Committee or the Company and, in the event that any amount or benefit under this Agreement or the Plan becomes subject to penalties under Section 409A of the Code, responsibility for payment of such penalties shall rest solely with the affected Directors and not with the Company.

17. Successors and Assigns. Except to the extent specifically limited by the terms and provision of this Agreement, this Agreement shall be binding upon and inure to the benefit of the parties hereto and their respective successors, assigns, heirs, and personal representatives.

18. Titles, Captions and Sections. Titles and captions contained in this Agreement are inserted for convenience of reference only and do not constitute a part of this Agreement for any other purpose. References to Sections in this Agreement refer to Sections of this Agreement unless otherwise stated.

19. Execution. This Agreement may be executed in two or more counterparts, all of which when taken together shall be considered one and the same agreement and shall become effective when counterparts have been signed by each party and delivered to the other party, it being understood that both parties need not sign the same counterpart. In the event that any signature is delivered by facsimile transmission or by email delivery of a "pdf" format data file, such signature shall create a valid and binding obligation of the party executing (or on whose behalf such signature is executed) with the same force and effect as if such facsimile or "pdf" signature page were an original thereof.

20. Further Assurances. Each party hereto shall do and perform (or shall cause to be done and performed) all such further acts and shall execute and deliver all such other agreements, certificates, instruments and documents as either party hereto reasonably may request in order to carry out the intent and accomplish the purposes of this Agreement and the Plan and the consummation of the transactions contemplated thereunder.

21. Severability. If any provision of this Agreement is held to be illegal or invalid for any reason, the illegality or invalidity shall not affect the remaining provisions hereof, but such provision shall be fully severable and this Agreement shall be construed and enforced as if the illegal or invalid provision had never been included herein.

22. Failure to Enforce Not a Waiver. The failure of the Company or Director to enforce at any time any provision of this Agreement shall in no way be construed to be a waiver of such provision or of any other provision hereof.

[*Remainder of Page Intentionally Left Blank. Signature Page Follows.*]

IN WITNESS WHEREOF, the parties to this Agreement have executed this Agreement effective as of the Grant Date.

PARTICIPANT:

_____

Name: [_____]

DIFFUSION PHARMACEUTICALS INC.

_____

By: William Elder

Title: General Counsel

By execution of this Agreement, Director acknowledges having received a copy of the Plan.

Exhibit 21.1

SIGNIFICANT 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%
Diffusion Pharmaceuticals LLC	VA	100%

Exhibit 23.1

Consent of Independent Registered Public Accounting Firm

We consent to the incorporation by reference in the registration statements (No. 333-206408, No. 333-206409, No. 333-218060, No 333-226782, No. 333-233381, No. 333-238233, and No. 333-258760) on Form S-8, (No. 333-222203, No. 333-233686, No. 333-234234, No 333-235670, and No. 333-238818) on Form S-1, and (No. 333-218062, No. 333-222879, No. 333-231541, and No. 333-249057) on Form S-3 of our report dated March 18, 2022, with respect to the consolidated financial statements of Diffusion Pharmaceuticals Inc.

/s/ KPMG LLP

McLean, Virginia
March 18, 2022

Exhibit 31.1

CERTIFICATION OF PRINCIPAL EXECUTIVE OFFICER PURSUANT TO SECTION 302 OF THE SARBANES OXLEY ACT OF 2002 AND SEC RULE 13a-14(a)

I, Robert J. Cobuzzi, Jr., Ph.D., 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(s) 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(s) 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 18, 2022

/s/ Robert J. Cobuzzi, Jr., Ph.D.

Robert J. Cobuzzi, Jr., Ph.D.
President and Chief Executive Officer
(Principal Executive Officer)

Exhibit 31.2

CERTIFICATION OF PRINCIPAL FINANCIAL OFFICER PURSUANT TO SECTION 302 OF THE SARBANES OXLEY ACT OF 2002 AND SEC RULE 13a-14(a)

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(s) 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(s) 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 18, 2022

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

Exhibit 32.1

CERTIFICATION OF PRINCIPAL EXECUTIVE OFFICER 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, 2021 as filed with the Securities and Exchange Commission on the date hereof (the "Report"), we, Robert J. Cobuzzi, Jr., Ph.D. and William K. Hornung, President 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.

/s/ Robert J. Cobuzzi, Jr., Ph.D
Robert J. Cobuzzi, Jr., Ph.D
President and Chief Executive Officer
March 18, 2022

/s/ William K. Hornung
William K. Hornung
Chief Financial Officer (Principal Financial and Accounting Officer)
March 18, 2022