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, 2020
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)
1317 Carlton Avenue, Suite 200	
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, 2020 (the last business day of the registrant's second fiscal quarter), was approximately $62.4 million.

As of March 12, 2021, 101,903,979 shares of common stock of the registrant were outstanding.

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the registrant's definitive Proxy Statement on Schedule 14A for its 2021 Annual Meeting of Stockholders are incorporated by reference into the indicated parts of this Form 10-K, as specified in the responses to the item numbers involved. Such Proxy Statement will be filed within 120 days after December 31, 2020, the end of the fiscal year to which this Annual Report relates.

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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
ANDA	abbreviated new drug application
Annual Report	this Annual Report on Form 10-K
API	active pharmaceutical ingredient
ARDS	acute respiratory distress syndrome
ASC	Accounting Standard Codification of the FASB
ASC 740-10	ASC Subtopic 740-10, *Accounting for Uncertainty of Income Taxes*
ASC 815-40	ASC 815-40, *Derivatives and Hedging, Contracts in an Entity's Own Equity*
ASUs	Accounting Standards Updates of the FASB
ASU 2018-07	ASU 2018-07, *Compensation--Stock Compensation (Topic 718): Improvements to Non-employee Share Based Payment Accounting*
Black-Scholes Model	Black-Scholes-Merton derivative investment instrument pricing model
Board	our board of directors
Bylaws	the Company's bylaws, as amended
COVID-19	Corona Virus Disease 2019, the novel coronavirus disease known as COVID-19, caused by SARS-CoV-2 infection
cGMP	current good manufacturing practices
CMO	contract manufacturing organization
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
ETASU	elements to assure safe use
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
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
IMM	irreversible morbidity and mortality
IND	investigational new drug application
IPR&D	in-process research and development
IRB	institutional review board
January 2018 Offering	our public offering and sale of 1,131,375 shares of common stock and warrants to purchase up to 1,131,375 shares of common stock completed in January 2018
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	Nasdaq Stock Market, LLC
NDA	new drug application
NIID	National Institute of Infectious Diseases in Bucharest, Romania
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
PaO2	partial pressure of blood oxygen
Planned Phase 2 Hypoxia-related Indication Trial	a Phase 2, controlled, clinical outcome study evaluating TSC in one or more appropriate hypoxiarelated indications that we intend to initiate assuming success in one or more of the TSC Oxygenation Trials
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
Proxy Statement	our definitive proxy statement on Schedule 14A for our 2021 Annual Meeting of Stockholders, to be filed with the SEC within 120 days after December 31, 2020, the end of the fiscal year to which this Annual Report relates
R&D	research and development
Regulation S-K	Regulation S-K promulgated under the Securities Act
REMS	risk evaluation and mitigation strategy
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2, the virus responsible for COVID-19
SEC	U.S. Securities and Exchange Commission
Securities Act	Securities Act of 1933, as amended
SOX	Sarbanes-Oxley Act of 2002, as amended
Tax Code	U.S. Internal Revenue Code of 1986, as amended
TCOM	transcutaneous oxygen measurement

tPA	tissue plasminogen activator
TSC	trans sodium crocetinate
TSC COVID Trial	our Phase 1b clinical trial evaluating TSC in hospitalized COVID-19 patients, completed in February 2021
TSC DLCO Trial	our planned Phase 2a clinical trial evaluating the effects of TSC through the measure of DLCO through the lungs as a surrogate measure of oxygen transfer efficiency in patients with previously diagnosed interstitial lung disease who have a baseline DLCO test that is abnormal
TSC GBM Trial	our Phase 3 clinical trial evaluating TSC in a newly diagnosed inoperable GBM patient population initiated in December 2017
TSC Induced Hypoxia Trial	our planned Phase 1b clinical trial evaluating the effects of TSC on VO2 and PaO2 in normal healthy volunteers exposed to conditions that induce hypoxia
TSC Oxygenation Trials	collectively, the TSC TCOM Trial, the TSC Induced Hypoxia Trial, and the TSC DLCO Trial
TSC Stroke Trial	our Phase 2 clinical trial evaluating TSC in the treatment of acute ischemic or hemorrhagic stroke, initiated in October 2019
TSC TCOM Trial	our planned Phase 1b clinical trial evaluating the effects of TSC on peripheral tissue oxygenation in healthy normal volunteers using a TCOM device, which we expect to commence before the end of March 2021
U.S.	United States
USPTO	U.S. Patent and Trademark Office
VO2	maximal oxygen consumption

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:

- 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;
- 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;
- 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;
- obtaining and maintaining intellectual property protection for our product candidates and our proprietary technology;
- our ability to operate our business without infringing the intellectual property rights of others and the potential for others to infringe upon our intellectual property rights;
- our failure to recruit or retain key scientific or management personnel or to retain our executive officers;
- 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 estimates regarding expenses, future revenues, capital requirements, and needs for additional financing;
- regulatory developments in the U.S., E.U., and other foreign jurisdictions;
- 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;
- any significant breakdown, infiltration, or interruption of our information technology systems and infrastructure;
- 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;
- 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 in *Part I - Item 1A. - Risk Factors* of 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 Stock Splits

Unless the context otherwise requires, in this Annual Report, all share and per share amounts related to our common stock give effect to (i) our 1-for-15 reverse stock split effective December 13, 2018 and (ii) our 1-for-10 reverse stock split effective August 17, 2016.

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 an innovative 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.

In addition to TSC, our product candidate DFN-529, a novel, allosteric PI3K/Akt/mTOR pathway inhibitor, is in early-stage development. We previously completed two Phase 1 clinical trials evaluating DFN-529 in age-related macular degeneration. DFN-529 was also previously in preclinical development in oncology, specifically GBM.

Highlights from 2020 and Early 2021

- ***Board & Management Additions and Changes*** - During the second half of 2020, our leadership team changed significantly. We appointed our new chief executive officer, Robert J. Cobuzzi, Jr., Ph.D., and our new general counsel, William Elder, in September 2020, followed by our new chief medical officer, Christopher Galloway, M.D., in October 2020. We also welcomed a new director, Jane Hollingsworth, to our Board in August 2020. Dr. Cobuzzi joined the Board in January 2020.

- ***Initiation and Completion of TSC COVID Trial*** - In September 2020, we announced the dosing of the first two patients in our TSC COVID Trial evaluating TSC in hospitalized COVID-19 patients at the NIID in Bucharest, Romania. On February 9, 2021, we completed dosing of the twenty-fourth and final patient in the TSC COVID Trial. No dose-limiting toxicities or serious adverse events were observed among any patients in the study, including those who received the highest dose of 1.5 mg/kg every 6 hours. Evaluation of secondary endpoint data is ongoing and we anticipate this data will be available early in the second quarter of 2021.

- ***February 2021 Equity Offering & Selected Unaudited Financial Information*** - During the first quarter of 2021, we completed the February 2021 Offering resulting in aggregate gross proceeds to the Company of approximately $34.5 million, before deducting underwriting discounts and commissions and offering expenses payable by us. In addition, during the period from January 1, 2021 through March 15, 2021, certain holders of warrants to purchase common stock cash exercised those warrants resulting in aggregate gross proceeds to the Company of approximately $2.2 million. As a result, combined with our cash and cash equivalents as of December 31, 2020 of $18.5 million, we expect that our existing cash and cash equivalents will enable us to fund our operating expenses and capital expenditures (including our planned clinical trials) through 2023.

Our Strategic Priorities for 2021

Since the founding of Diffusion LLC, we have been principally focused 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. Prior to 2020, these efforts generated a substantial amount of data related to TSC, including data related to chemistry, manufacturing, and controls, preclinical safety and/or efficacy data in a wide array of experimental models, single dose safety, tolerability, and pharmacokinetic data, and clinical data and other information related to TSC's potential as a supplement to standard-of-care treatment in GBM, peripheral artery disease, and stroke.

In March 2020, the COVID-19 pandemic accelerated in the U.S. resulting in numerous delays and other challenges for biopharmaceutical companies conducting clinical studies in indications not related to COVID-19, including our TSC Stroke Trial. In early April 2020, we announced plans to initiate a clinical research program to evaluate TSC in patients with COVID-19 due to the anticipated persistence of the COVID-19 pandemic coupled with our belief in the potential of TSC to improve low tissue oxygen levels, a common symptom and complicating factor in the treatment of COVID-19. We believe this decision was both opportunistic and a natural extension of the previous development work conducted with TSC, and in September 2020 we commenced the TSC COVID Trial.

In November 2020, we announced that, following changes to our management team in the prior two months, we had initiated a thorough review of our then-existing development program for TSC and commenced plans to modify the program with the intent of accomplishing two principal strategic objectives:

- To optimize the clinical dose and dosing frequency for TSC.

- To evaluate TSC in clinical models designed to establish proof of concept for improvement in oxygenation.

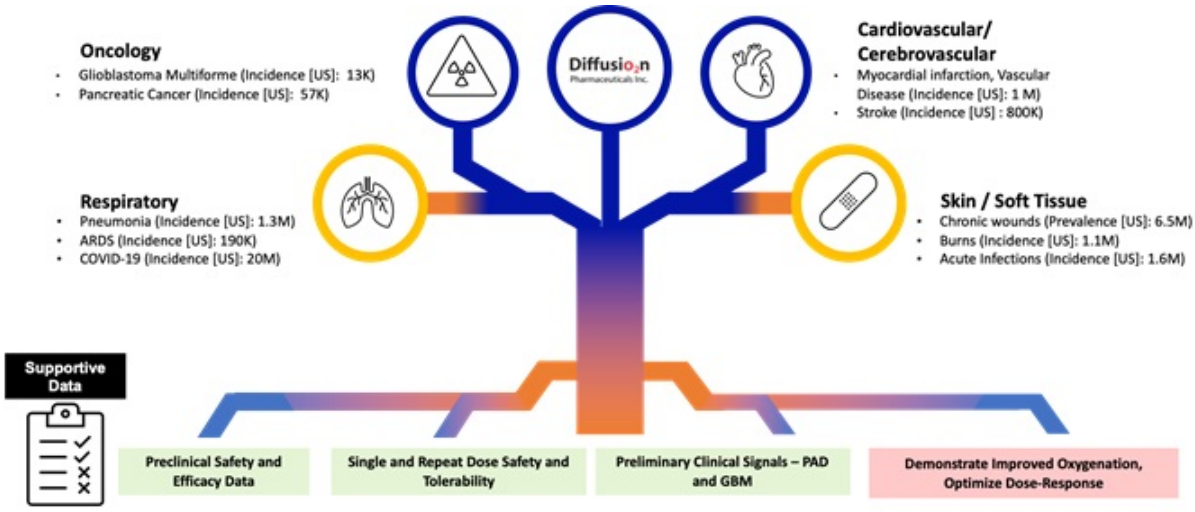
The completion of the TSC COVID Trial in February 2021 provided the first multiple daily dose safety and tolerability data for TSC. We expect corresponding pharmacokinetic and other secondary endpoint data from this trial to be available early in the second quarter of 2021. Obtaining these data represents the first, major step in our ongoing efforts to implement our modified development strategy, intended to strategically gap-fill, supplement, and expand on our past development work in TSC, with the ultimate goal of maximizing the probability of regulatory approval and, if TSC is approved, commercial success.

During the next twelve months, we intend to continue to execute our strategy and accomplish the following principal, strategic objectives, all of which we expect to be able to fund with cash-on-hand:

- ***Complete the TSC Oxygenation Trials*** – As described in more detail under the heading, *— Our Lead Product Candidate: Trans Sodium Crocetinate — Our Anticipated Next Steps in the TSC Development Program: The TSC Oxygenation Trials*, the next phase in our development plan is to evaluate TSC's effects in clinical models of oxygenation in an effort to establish a dose-response relationship. We expect to commence the TSC TCOM Trial before the end of March 2021 with data expected in the second quarter of 2021, and we intend to commence both the TSC DLCO Trial and TSC Induced Hypoxia Trial in the third quarter of 2021 with data expected from each study expected within two months of their respective completion.

- ***Initiate Phase 2 Trial of TSC in Hypoxia-related Indication*** – We believe positive data from one or more of the three TSC Oxygenation Trials would provide definitive evidence of TSC's enhancement of oxygenation, whether through increased uptake in the lungs, enhanced delivery, increased utilization at the tissue level, or some combination thereof. Positive data from any of these studies, if obtained, will guide the subsequent steps of our development strategy focused on demonstrating the clinical and therapeutic benefits of TSC in relevant patient populations on the hypoxia continuum. In particular, if successful in one or more of the three TSC Oxygenation Trials, we intend to initiate a Phase 2, controlled, clinical outcome study evaluating TSC in one or more appropriate hypoxia-related indications, which we refer to as our Planned Phase 2 Hypoxia-related Indication Trial, in the first quarter of 2022.

- ***Continue to Improve Our Efficiency and Effectiveness*** – This will include evaluating, refining, and improving our policies, procedures, and processes related to chemistry, manufacturing, and controls, quality assurance, information technology, intellectual property, human capital, and other areas, including as described in more detail under the headings, *— Products, Product Development, and Our Competition* and *— Our People and Human Capital Resources*.



Representation of data supporting the potential use of TSC for the treatment of certain medical conditions complicated by hypoxia. Incidence numbers represent annual incidence in U.S. as reported by U.S. Centers for Disease Control and Prevention and other publicly available sources.

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 associated with the pathophysiology of many acute and chronic conditions including cancers, heart attack, stroke, ARDS, skin and soft tissue diseases, neurodegenerative diseases and other intractable and difficult-to-treat conditions, further complicating treatment of the underlying condition by medical providers.

Hypoxia: A Key Driver of Unmet Medical Needs

Oxygen is fuel for life. The constant uptake and delivery of oxygen within our body is necessary to sustain life whether at rest or under stress, in sickness and in health.

Normally, the body's supply of oxygen sustains life by meeting the demand for oxygen at the cellular level. This availability of sufficient oxygen enables efficient and sustainable generation of energy to support the metabolic demands of the cells. Low oxygen content in the blood stream, also known as hypoxemia, often leads to hypoxia, a condition in which a region of the body's tissues is deprived of sufficient oxygen to produce the energy it needs to survive. This state can only be sustained for very brief periods of time, sometimes just minutes, before the body tissue experiences ischemia, damage, and, eventually, cellular death.

Under normal conditions, when oxygen is inhaled through the lungs it diffuses from this area of high oxygen concentration in the air sacs of the lungs, or alveoli, into pulmonary circulation where the oxygen concentration is lower. This diffusion process is passive. Oxygen moves across cell layers and vessel walls into the blood stream in a manner that does not require energy and avoids over-oxygenating the body. Once oxygen reaches the blood stream, it is rapidly taken up onto our red blood cells while a very small amount dissolves in the plasma. The hemoglobin within the red blood cells act as mass transport carriers for oxygen. Red blood cells are pumped throughout our circulatory system by the heart, reaching every cell in our body. Upon reaching its cellular destination, the oxygen is released from the hemoglobin and again passively diffuses from the area of high concentration in the bloodstream to the lower concentration areas in the tissues.

Our body's ability to deliver sufficient oxygen in this manner is determined by several factors, including the amount of oxygen in the air we breathe, our cardiac output (i.e., how well the heart circulates the oxygen), our hemoglobin content (i.e., how many transporters there are to carry the oxygen), and the level of oxygen saturation of hemoglobin, which can carry up to four oxygen molecules. A variety of medical interventions are available to augment or supplement these factors in the oxygen delivery process in order to increase mass oxygen delivery. For example, there are medications and mechanical pumps designed to improve cardiac output, blood transfusions to increase hemoglobin content in the blood, and other passive and mechanical methods to increase the systemic availability of oxygen. However, while these existing strategies can be very effective in certain circumstances, they do not specifically focus on enhancing the diffusion process by which oxygen moves from a high concentration area in the bloodstream to a lower concentration are in hypoxic tissue. Accordingly, we believe there remains a significant unmet need in the treatment of hypoxia.

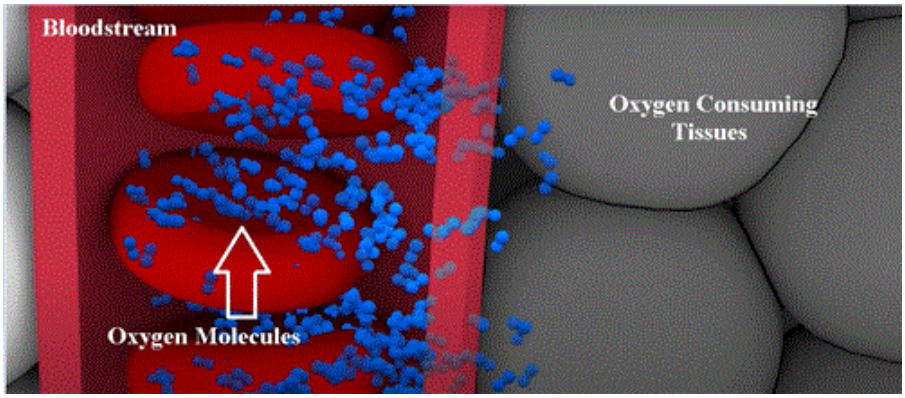
An additional, important factor in oxygen uptake and delivery is how efficiently the oxygen moves or diffuses across the many impediments that can slow the movement of oxygen through the body, such as the red blood cell walls, water molecules in plasma, cellular layers of the blood vessels, and other tissues. Currently, there is no well-known or widely-used medical method to augment or supplement this factor in the oxygen delivery process.

TSC: A Novel Mechanism of Action and Demonstrated Safety Profile

We believe that TSC's novel mechanism of action would be the first therapy specifically designed to enhance the oxygen diffusion process, thereby supporting normal, physiologic levels of oxygen diffusion at the uptake and delivery points.

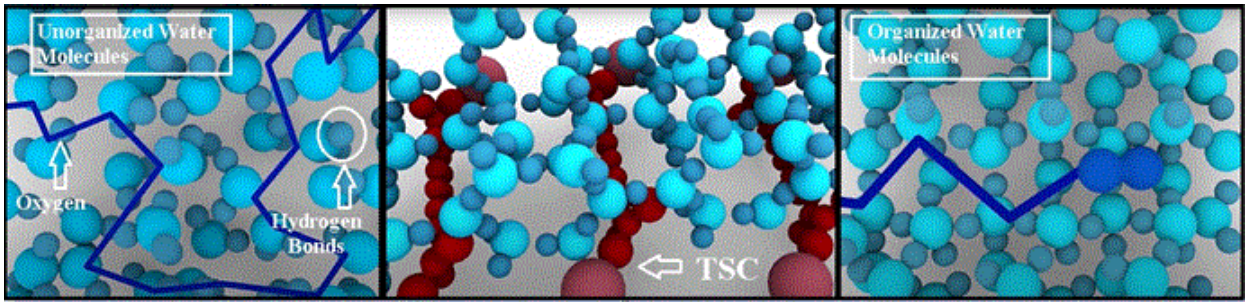
TSC's Novel Mechanism of Action

Blood plasma is approximately 90.0% water and these water molecules are constantly moving, bound together in a loosely organized matrix by hydrogen bonds. Due to oxygen's passive diffusion process through the plasma from areas of high oxygen concentration to areas of low oxygen concentration, a treatment that can reduce the factors that resist this movement should make oxygen more available to hypoxic tissues.



Representation of oxygen molecules moving from red blood cells, across the concentration gradient, to oxygen-consuming tissues.

TSC was designed to enhance the level of organization among 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. In animal models, this diffusion-enhancing mechanism of action has been observed to affect hypoxic tissue preferentially while avoiding excessive oxygen-related tissue toxicity, also known as hyperoxia.



Representation of the indirect course of oxygen molecule movement through "unorganized" or randomly moving water molecules (left panel) versus the more direct path through "organized" molecules allowed by TSC (right panel).

TSC's Clinical Safety Profile

TSC has been observed to be safe and well-tolerated at most doses tested in over 180 subjects included to-date in clinical studies. A maximum tolerated dose was identified in the initial clinical study of TSC conducted in normal healthy volunteers, and subsequent clinical studies have been conducted with lower doses. These studies have included patients with variety of medical conditions often complicated by hypoxia, including our clinical studies conducted in patients afflicted with GBM, peripheral artery disease with intermittent claudication, stroke, and, most recently, COVID-19. 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.

In the TSC COVID Trial, which we completed in February 2021, we evaluated the safety and tolerability of TSC administered on a more frequent dosing regimen than had been previously tested in a clinical trial setting. No dose-limiting toxicities or serious adverse events were observed among any patients in the TSC COVID Trial, including those who received the highest tested dose of TSC, 1.5 mg/kg administered intravenously every six hours for a period of at least five and up to 15 days.

TSC's Potential to Treat Hypoxia-Related Conditions

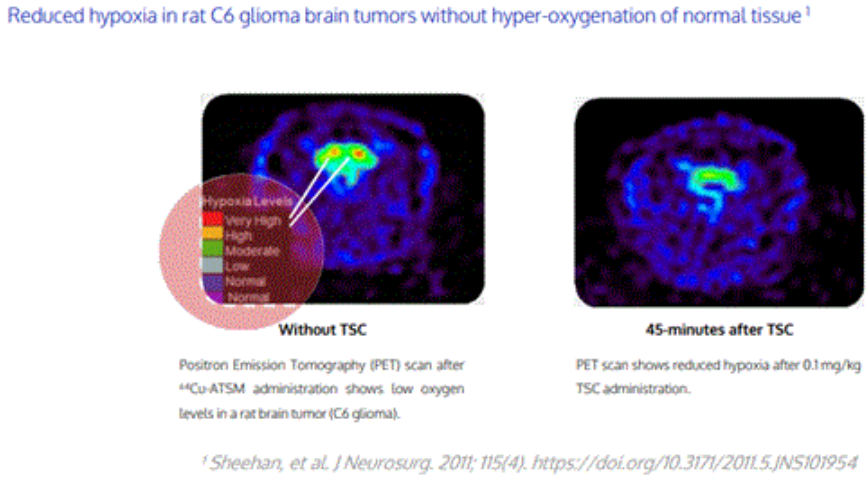
Hypoxia is a critical, complicating factor in many intractable and difficult-to-treat conditions affecting people of all ages, including cancers, cardiovascular disease, stroke, respiratory disease including ARDS, skin and soft tissue diseases, and neurodegenerative diseases. We have previously evaluated TSC in a variety of preclinical and clinical studies. We believe that the data we have obtained through certain preclinical studies provide support for TSC's ability to improve oxygenation, while data obtained through the clinical trials we have undertaken to date suggest TSC is safe and well-tolerated at the doses tested, including administration of TSC to more than 180 human subjects and patients with GBM, acute stroke, COVID-19, acute lung injury, and peripheral artery disease with intermittent claudication.

Clinical and Preclinical Development of TSC to Date

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 number of positive effects have been observed in connection with TSC administration, including:

- Reducing hypoxia in rat brain tumors without hyper-oxygenation of normal tissue.



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

- Improving survival in a rat brain tumor model when added to radiotherapy, whether or not combined 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 tPA at one-hour post-clot infection and with tPA at three hours post-clot infection.

- Improving arterial PaO2 levels in a rat model of ARDS.

Glioblastoma Multiforme

We believe TSC may be able to benefit cancer patients by re-oxygenating hypoxic cancer tissue, making the cells more susceptible to the therapeutic effects of standard-of-care radiation therapy and chemotherapy. In particular, GBM is an especially deadly form of brain cancer that each year affects approximately 12,000 patients in the U.S. and approximately 35,000 patients worldwide, and for which TSC has received an Orphan Drug Designation from the FDA.

We previously completed a Phase 2 clinical trial that evaluated 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.

Based upon data from the inoperable patient subgroup in the Phase 2 trial and guidance from the FDA received at our End-of-Phase-2 meeting, we initiated the TSC GBM Trial in the newly diagnosed inoperable GBM patient population in December 2017. The TSC GBM Trial was designed to enroll 236 patients in total, with 118 in the treatment arm and 118 in the control arm. The trial began with an FDA-mandated, open-label, dose-escalation safety run-in for which enrollment was completed and has closed. A total of 19 patients were enrolled in an attempt to ensure that at least 8 patients completed the FDA-specified 42-month exposure period. At a meeting in the third quarter of 2019, the data safety monitoring board for the trial concluded that no adverse safety signal was present and unanimously recommended the trial continue as planned, with TSC to be used in combination with temozolomide, an anti-cancer chemotherapy drug, during the adjuvant treatment chemotherapy period. However, we determined we did not have adequate resources at the time to fully support the randomized portion of the TSC GBM Trial and commencement of enrollment in the randomization portion of the TSC GBM Trial was suspended. Further consideration of if, when, and how to continue the development of TSC as a treatment for GBM — including any restart of the TSC GBM Trial — will take place following completion of the TSC Oxygenation Trials.

Stroke

We believe TSC has potential applications in both ischemic and hemorrhagic stroke through mitigation of stroke-induced hypoxia and related damage to brain tissue. A stroke occurs when blood flow to the brain is blocked, referred to as an ischemic stroke, or a blood vessel in the brain ruptures, referred to as a hemorrhagic stroke, causing damage to surrounding brain tissue. According to the U.S. Centers for Disease Control and Prevention, stroke is the fifth leading cause of death and a leading cause of adult disability in the U.S. The hypoxic conditions in the brain of stroke patients may be a significant factor contributing to morbidity and mortality and, based upon certain preclinical safety and efficacy data and additional clinical safety data, we believe TSC could enhance the diffusion of oxygen into brain tissue to reduce stroke-induced hypoxia and neuronal death.

In October 2019, we began enrolling patients in our TSC Stroke Trial, a randomized Phase 2 trial designed to evaluate TSC in the treatment of acute ischemic or hemorrhagic stroke. The TSC Stroke Trial was planned to enroll 160 total patients, evenly split between the TSC treatment arm and the control arm, with all patients to receive TSC or placebo treatment, as applicable, while in the ambulance to ensure treatment as soon as possible after the onset of clinical symptoms. However, due to a variety of factors, including challenges related to the trial's on-ambulance treatment design and overall healthcare system capacity related to the onset of the COVID-19 pandemic during the first half of 2020, we voluntarily terminated the TSC Stroke Study in the second half of 2020 in order to prioritize resources to shorter duration studies, including the TSC COVID Trial and the TSC Oxygenation Trials. Further consideration of if, when, and how to continue the development of TSC as a treatment for stroke will take place following completion of the TSC Oxygenation Trials.

COVID-19

We believe TSC's oxygen-enhancing mechanism could potentially provide benefit to patients with low oxygen levels at risk of developing ARDS and multiple organ failure, such as patients with COVID-19.

On September 10, 2020, we announced the dosing of the first two patients in our TSC COVID Trial evaluating TSC in hospitalized COVID-19 patients at the NIID in Bucharest, Romania. The primary endpoint of the TSC 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.

On February 9, 2021, we completed dosing of the twenty-fourth and final patient in the TSC COVID Trial. No dose-limiting toxicities or serious adverse events were observed among any patients in the study, including those who received the highest dose of 1.5 mg/kg every 6 hours. Evaluation of secondary endpoint data is ongoing and we anticipate this data will be available early in the second quarter of 2021. Further consideration of if, when, and how to continue the development of TSC as a treatment for COVID-19 — including any commencement of enrollment in the previously announced Phase 2b portion of the TSC COVID Trial — will take place following completion of the TSC Oxygenation Trials.

Our Anticipated Next Steps in the TSC Development Program: The TSC Oxygenation Trials

Following completion of the TSC COVID Trial in February 2021, the next step we have planned in the development of TSC is the design and execution of a trilogy of clinical studies using short-term, experimental models to evaluate the clinical effects of TSC on oxygenation. As of March 15, 2021, TSC has been administered to more than 180 subjects in our clinical trials. Data from these clinical trials have contributed significantly to our understanding of the safety, tolerability, and pharmacokinetics of TSC. In addition, post hoc analyses of two of our prior studies involving patients with peripheral artery disease with claudication and unresected GBM tumors have provided preliminary signals suggesting TSC's effect on oxygenation. However, neither of these studies was statistically powered to formally evaluate efficacy, and we therefore believe that further, robust clinical development of TSC requires a prospective exploration of the relationship between the level of exposure (dose) and response (change in oxygenation).

To this end, we plan to execute three short-term clinical trials during 2021, each of which we expect to conduct in the U.S. and fund with cash-on-hand. We believe positive data from any one or more of the three TSC Oxygenation Trials would provide evidence of a definitive effect of TSC on oxygenation, whether through increased uptake in the lungs, enhanced delivery, increased utilization at the tissue level, or some combination thereof. Positive data from any of these studies, if obtained, will also guide the subsequent steps of our development strategy focused on demonstrating the clinical and therapeutic benefits of TSC in relevant patient populations across the hypoxia continuum.

The TSC TCOM Trial: TSC's Effects on Peripheral Tissue Oxygenation

The first of the three Oxygenation Trials is the TSC TCOM Trial, which we expect to initiate before the end of March 2021. The TSC TCOM Trial is designed as a double-blind, randomized, placebo-controlled study in healthy volunteers breathing 100.0% oxygen. The study is designed to evaluate the effects of TSC on peripheral tissue oxygenation using a TCOM device. The TCOM device directly measures the release of oxygen from the blood vessels through the skin and is commonly used to predict the likelihood of wound healing, the potential for success with hyperbaric therapy, and to map the appropriate location for limb amputation. The TSC TCOM Trial will test single, ascending doses of TSC in an attempt to establish the exposure-response relationship between TSC and enhanced oxygen delivery and will be statistically powered to evaluate the difference in tissue oxygenation levels versus placebo. We anticipate this study will be completed in the second quarter of 2021, with topline results available within two months following study completion.

The TSC Induced Hypoxia Trial: TSC's Effects Under Induced Hypoxic Conditions

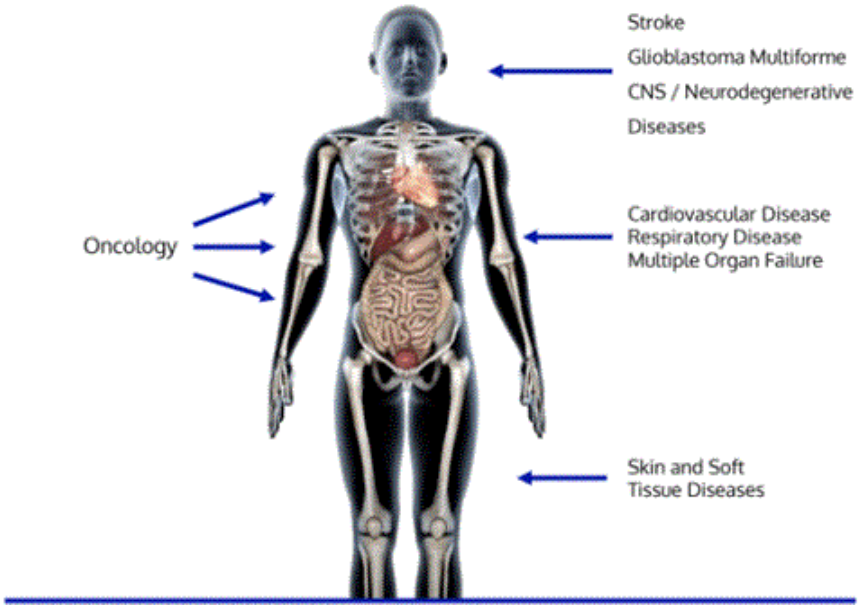
The second TSC Oxygenation Trial is our planned TSC Induced Hypoxia Trial, which we expect to initiate in the third quarter of 2021. The TSC Induced Hypoxia Trial is expected to be a double-blind, randomized, placebo-controlled study which will evaluate the effects of TSC on maximal oxygen consumption, or VO2, and partial pressure of blood oxygen, or PaO2, in normal healthy volunteers exposed to simulated altitude conditions that induce hypoxia. Subjects in the TSC Induced Hypoxia Trial will be subjected to incremental levels of physical exertion while exposed to hypoxic and hypobaric conditions. The primary endpoints in the TSC Induced Hypoxia Trial will be change from baseline in VO2 and PaO2 after receiving a single intravenous dose of TSC. The study will be statistically powered to evaluate the difference in effect of escalating doses of TSC versus placebo in an attempt to establish a dose-response relationship on oxygen consumption and availability. We anticipate this study will be completed in the second half of 2021, with topline results available within two months of study completion.

The TSC DLCO Trial: TSC's Effects on Oxygen Transfer Efficiency

The third TSC Oxygenation Trial is our planned TSC DLCO Trial, which we expect to initiate in the third quarter of 2021. The TSC DLCO Trial is expected to be a double-blind, randomized, placebo-controlled study which will evaluate the effects of TSC on the diffusion of carbon monoxide through the lungs, also known as DLCO, in patients with previously diagnosed interstitial lung disease who have a baseline DLCO test result that is abnormal. DLCO testing is commonly performed as part of standard pulmonary function testing and aids in the diagnosis or dyspnea, also known as shortness of breath, as well as to track improvement or progression over time on prescribed treatments. In the TSC DLCO Trial, DLCO will act 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 TSC DLCO Trial TSC will test single, ascending doses of TSC in an attempt to establish the exposure-response relationship between TSC and oxygen transfer efficiency. The study will be statistically powered to evaluate the difference in effect of TSC on improvement in DLCO versus placebo. We anticipate this study will be completed in the second half of 2021, with topline results available within two months of study completion.

Anticipated Next Steps Following Completion of the TSC Oxygenation Trials

Assuming success in one or more of the three TSC Oxygenation Trials, we expect to identify and announce the specific, hypoxia-related indications we will target in advancing TSC's development in the fourth quarter of 2021 and intend to initiate our Planned Phase 2 Hypoxia-related Indication Trial in the first quarter of 2022.



Certain medical conditions complicated by hypoxia.

Our Second Product Candidate: DFN-529

Our product candidate DFN-529 is a novel PI3K/Akt/mTOR pathway inhibitor which has completed two Phase 1 clinical trials for age-related macular degeneration and was previously in preclinical development in oncology, specifically for GBM. DFN-529 has shown activity in both in vitro and in vivo GBM animal models and has been demonstrated to be orally bioavailable and capable of crossing the blood brain barrier. We are currently in discussions with multiple third-party research scientists regarding the potential initiation of further studies to evaluate the effects of DFN-529 in preclinical cancer models. We believe these additional data may help guide us in choosing an appropriate clinical development pathway for DFN-529. We also continue to explore business options for DFN-529, including out-licensing opportunities and other strategic partnerships.

Products, Product Development, and Our Competition

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, 2020, we incurred approximately $9.4 million in costs related to research and development of our products, an increase of approximately $2.8 million compared to the year ended December 31, 2019. The majority of these costs were related to the development of TSC and related personnel, including costs associated with the TSC COVID Trial, which commenced in September 2020 and was completed in February 2021, as well as the wind down of the TSC Stroke Trial, which commenced in October 2019 and was terminated in the second half of 2020.

We expect this trend to continue for the foreseeable future, including planned expenditures related to the TSC Oxygenation Trials and other costs associated with the conduct of additional, supportive preclinical studies and general research and development activities related to TSC. We intend to focus the remainder of our foreseeable research and development expenditures will on the development of DFN-529, including additional preclinical studies evaluating DFN-529 in cancer models that we are in the early stages of planning.

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.

Our 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, 2020, we owned 16 issued U.S. patents and 36 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. Additional information regarding patent term extensions can be found under the heading, see *— 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 certain rights of exclusivity under certain FDA regulations. Additional information regarding orphan and ultra-orphan can be found under the heading, see *— Government Regulation — Certain Other FDA Regulations — The Orphan Drug Act of 1983*.

Materials and Manufacturing

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 in *Part I – Item 1A. Risk Factors – Risks Related to the Development, Regulatory Approval, and Commercialization of TSC and Our Other Product Candidates*.

Our 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 products, therapeutics, or devices that may nevertheless be competitive with TSC, if approved, including NuvOx Pharma LLC, Hemoglobin Oxygen Therapeutics LLC, and Cardax, 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 particular 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, DFN-529, 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 and DFN-529.

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, DFN-529, 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 and Other Post-Approval Requirements*. 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 50.0% 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 with respect to the t

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) rare diseases or conditions 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 ETASU, or elements to assure safe use. ETASU 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 TSC COVID Trial at the NIID 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 Affordable Care Act 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 Centers for Medicare & Medicaid Services, 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 Affordable Care Act 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 this or any similar legislation in the future may result in a similar reduction in payments from non-governmental payors.

- The Physician Payments Sunshine Act - The Physician Payments 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

Employees

As of December 31, 2020, we had 12 full-time employees and one part-time employee, up from 12 employees as of December 31, 2019, and as of March 15, 2021, we have added one additional full-time employee in 2021. 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 80.0% employer contribution to family medical coverage), health savings accounts with a company contribution, 25 days of paid leave, the 401(k) plan, flexible work schedules, and other benefits.

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, Wellness, and Our Response to COVID-19

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.

During 2020, in response to the COVID-19 pandemic, we took 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.

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." Our principal corporate office is located at 1317 Carlton Avenue, Suite 200, 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 effect 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 effect 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* of this Annual Report, 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 TSC 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, our Planned Phase 2 Hypoxia-related Indication Trial we intend to commence assuming success in the TSC Oxygenation Trials – 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. We are also in early-stage development of our second product candidate, DFN-529, and, 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 reason, 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 TSC Oxygenation Trials and our Planned Phase 2 Hypoxia-related Indication Trial we intend to commence assuming success in the TSC Oxygenation Trials, our ability to fund them;

- 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, or results of operations may be materially and adversely effected.

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, DFN-529, 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, or results of operations.

We currently have no products approved for sale, and we may never obtain regulatory approval to commercialize TSC, DFN-529, 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 effect our business, financial condition, or 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 at our partner 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 facility or equipment, communication breakdowns, or acts of God. For example, we are currently facing 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 primary CMO partner conducts significant portions of the TSC manufacturing process has been mandated to devote the majority of the facility's available resources to the manufacture of components of the COVID-19 vaccine. If our CMO is unable to manufacture sufficient quantities of drug supply to meet our needs in a timely fashion or in accordance with the specifications contracted for, we may be forced to delay our development plans for TSC, find alternative suppliers, or pursue other available remedies, which could result in additional costs and the diversion of management's time.

Amplifying this risk is the fact that we currently depend upon a sole source for manufacture of API for TSC and other aspects of our manufacturing process, limiting our available options to troubleshoot these issues. Although we are currently in the process of identifying and developing alternative manufacturing and supply alternatives, this process remains ongoing, will take time, and will involve significant costs. 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 product TSC, its API, and its other component parts. In order to meet these needs, our CMOs and suppliers will need to be able 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 products or product candidates or their components into the United States or other countries as a result of, among other things, regulatory agency approval requirements or import inspections, incomplete or inaccurate import documentation or defective packaging.

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 approved, commercial supply, and could result in significant, unanticipated costs or an ability to effectively develop our products candidates or commercialize our approved products on a timely basis, or at all, which could materially and adversely effect our business, financial condition, or 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 or a non-U.S. 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 the 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 effect our business, financial condition, or 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 effected 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 TSC COVID Trial, which we completed in February 2021, was conducted at the NIID 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 TSC 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 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 is 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 effected 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 withdrawal 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 in *Part I – Item 1. Business – Certain Other Legislation and Regulations – Current Healthcare Laws and Regulations* of this Annual Report. 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

Since the founding of Diffusion LLC in 2001, we have been principally focused 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. Many of our issued patents were issued early in our Company's history. While we are regularly engaged in further research and development activities with respect to TSC and our other product candidates that may result in novel developments and findings that ultimately lead to further intellectual property opportunities, if the terms of any of our key patents expire before or soon after our therapeutic candidates are approved, or if manufacturers of biosimilar drugs successfully challenge our patents, our business, financial condition, or results of operations may be materially adversely effected.

Patents have a limited duration. In the United States, if all maintenance fees are timely paid, the natural expiration of a patent is generally 20 years from its earliest non-provisional filing date in the U.S. Various extensions may be available, including under the Hatch-Waxman Amendments as described elsewhere in this Annual Report, but the life of a patent, and the protection it affords, is limited. Even if patents covering TSC and our product candidates, including with respect to their manufacture or use, are obtained, once the patent life has expired, we may be open to additional competition from competitive medications, including biosimilar medications. In the case of Diffusion, the normal lives (in other words, prior to the application of any patent term restoration of marketing exclusivity periods that may be available) of our issued U.S. patents related to TSC begin to expire in 2023, which may be prior to the time that we are able to obtain regulatory approval for and, if approved, commercialize TSC.

Even if patent term extension or other protections such as marketing exclusivity are available upon the regulatory approval (if any) of TSC or any of our other product candidates, the benefits provided by these regulatory and legislative mechanisms is limited and typically less robust than full patent protection. For example, the five-year extension of patent life potentially available under the Hatch-Waxman Amendments cannot extend the remaining term of a patent beyond a total of 14 years from the date of product approval, and only one patent applicable to an approved drug may be extended. Receiving such an extension is also subject to compliance with applicable deadlines for application and certain other regulatory requirements. Moreover, the length of the extension could be less than we request. If we are unable to obtain patent term extension or the term of any such extension is less than we request, the period during which we can enforce our patent rights for that product will be shortened and our competitors may obtain approval to market competing products sooner than we expect. Also, the scope of our right to exclude during any patent term extension period may be limited or may not cover a competitor's product or product use.

Given the amount of time required for the development, testing, and regulatory review of new drug candidates, patents protecting any drug candidate might expire before or shortly after such drug candidate is approved or commercialized. Similarly, our patents and patent applications may not provide us with sufficient time or rights to commercialize our product candidates or exclude others from commercializing products similar ours. If our patent protections for our product candidates have expired, this could include manufacturers of identical, biosimilar drugs.

If we are unable to obtain new, patent claims with respect to our existing product candidates and other technologies, in particular those related to our lead product candidate TSC, that both adequately protect our intellectual property position for commercial purposes and extend the term of overall protection as compared to our existing issued patents, we may be reliant on these types of patent term extensions and similar exceptions for such protection during the ultimate commercialization of TSC. This limited protection could have a material and adverse effect on our business, financial condition, or results of operations.

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 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. 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 United States 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 often 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. In particular, 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. If the other issued patents in our portfolio currently or that may issue in the future are not adequate to protect our technologies, our competitive position may be harmed and we may face generic or other competition sooner than we otherwise would.

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 effect our business, financial condition, or results of operations. For more information about our intellectual property and our competition, see the information included in *Part I – Item 1. Business – Products, Product Development, and Our Competition* of this Annual Report.

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 in *Part I – Item 1. Business – Government Regulation – The Hatch-Waxman Amendments* of this Annual Report.

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 infringe 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 effect our business, financial condition, or results of operations.

General Risks Related to Our Intellectual Property

Our business, financial condition, or results of operations may also be materially adversely effected 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, including expected costs related to the planned TSC Oxygenation Trials and our Planned Phase 2 Hypoxia-related Indication Trial, through 2023, we expect to continue to spend substantial amounts as we continue to develop TSC and our other product candidates, 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 TSC 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 13 full-time employees and one part-time employee, including our new Senior Director of Quality Assurance hired during the first quarter of 2021. 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 2021 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 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 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 in *Part I — Item 1. Business – Our People and Human Capital Resources* of this Annual Report

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, in the 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 my adversely effect 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 two product candidates under active development, our lead product candidate, TSC, and our second product candidates, DFN-529. 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 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, 2020, we had $11.7 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 50.0% 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 year ended December 31, 2019, as a result of the issuance of a significant number of shares our common stock pursuant to the May 2019 Offering, November 2019 Offering, and December 2019 Offering, we performed an analysis under Section 382 of the Tax Code and, as a result of such analysis and a determination that such an ownership change had taken place, we reduced our NOL carryforwards. 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 in *Part I – Item 1. Business – Certain Other Legislation and Regulations – Current Healthcare Laws and Regulations* of this Annual Report 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

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 or inability to meet the continued listing requirements of Nasdaq.

During the year ended December 31, 2020, the closing market price for our common stock varied between a high of $1.50 on July 21, 2020 and a low of $0.26 on March 16, 2020. 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 business, 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, or results of operations.

In addition, 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, maintaining a minimum closing bid price for our common stock. Particularly given the historical volatility experienced by our common stock, there is no assurance that we will continue to meet the minimum closing price requirement and other listing requirements of Nasdaq.

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 transaction 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 the TSC Oxygenation Trials, our Planned Phase 2 Hypoxia-related Indication Trial, and 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 33,658,538 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 arrangement could materially decrease any potential returns on our investment in TSC or our other product candidates, or otherwise materially and adversely effect 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 stockholder s.

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 would apply 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

Our principal executive office is located in a leased facility in Charlottesville, Virginia, where we lease approximately 8,000 square feet of office space for approximately $10,000 per month. The current term of our Charlottesville lease will expire in April 2022.

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, 2021, there were 353 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 business, 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 in *Part I – Item 1A. Risk Factors* of this Annual Report.

Diffusion Pharmaceuticals: Enhancing Oxygen, Fueling Life

We are an innovative 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.

In addition to TSC, our product candidate DFN-529, a novel, allosteric PI3K/Akt/mTOR pathway inhibitor, is in early-stage development. We previously completed two Phase 1 clinical trials evaluating DFN-529 in age-related macular degeneration. DFN-529 was also previously in preclinical development in oncology, specifically GBM.

Highlights from 2020 and Early 2021

- ***Board & Management Additions and Changes*** - During the second half of 2020, our leadership team changed significantly. We appointed our new chief executive officer, Robert J. Cobuzzi, Jr., Ph.D., and our new general counsel, William Elder, in September 2020, followed by our new chief medical officer, Christopher Galloway, M.D., in October 2020. We also welcomed a new director, Jane Hollingsworth, to our Board in August 2020. Dr. Cobuzzi joined the Board in January 2020.

- ***Initiation and Completion of TSC COVID Trial*** - In September 2020, we announced the dosing of the first two patients in our TSC COVID Trial evaluating TSC in hospitalized COVID-19 patients at the NIID in Bucharest, Romania. On February 9, 2021, we completed dosing of the twenty-fourth and final patient in the TSC COVID Trial. No dose-limiting toxicities or serious adverse events were observed among any patients in the study, including those who received the highest dose of 1.5 mg/kg every 6 hours. Evaluation of secondary endpoint data is ongoing and we anticipate this data will be available early in the second quarter of 2021.

- ***February 2021 Equity Offering*** - During the first quarter of 2021, we completed the February 2021 Offering resulting in aggregate gross net proceeds to the Company of approximately $34.5 million, before deducting underwriting discounts and commissions and offering expenses payable by us. In addition, during the period from January 1, 2021 through March l5, 2021, certain holders of warrants to purchase common stock cash exercised such warrants resulting in aggregate net proceeds to the Company of approximately $2.2 million. As a result, combined with our cash and cash equivalents as of December 31, 2020 of $18.5 million, we expect that our existing cash and cash equivalents will enable us to fund our operating expenses and capital expenditures (including our planned clinical trials) through 2023.

Our Strategic Priorities for 2021

Since the founding of Diffusion LLC, we have been focused 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. Prior to 2020, these efforts generated a substantial amount of data related to TSC, including data related to chemistry, manufacturing, and controls, preclinical safety and/or efficacy data in a wide array of experimental models, single dose safety, tolerability, and pharmacokinetic data, and clinical data and other information related to TSC's potential as a supplement to standard-of-care treatment in GBM, peripheral artery disease, and stroke.

In March 2020, the COVID-19 pandemic accelerated in the U.S. resulting in numerous delays and other challenges for biopharmaceutical companies conducting clinical studies in indications not related to COVID-19, including our TSC Stroke Trial. In early April 2020, we announced plans to initiate a clinical research program to evaluate TSC in patients with COVID-19 due to the anticipated persistence of the COVID-19 pandemic coupled with our belief in the potential of TSC to improve low tissue oxygen levels, a common symptom and complicating factor in the treatment of COVID-19. We believe this decision was both opportunistic and a natural extension of the previous development work conducted with TSC, and in September 2020 we commenced the TSC COVID Trial.

In November 2020, we announced that, following changes to our management team in the prior two months, we had initiated a thorough review of our then-existing development program for TSC and commenced plans to modify the program with the intent of accomplishing two principal strategic objectives:

- To optimize the clinical dose and dosing frequency for TSC.
- To evaluate TSC in clinical models designed to establish proof of concept for improvement in oxygenation.

The completion of the TSC COVID Trial in February 2021 provided the first multiple daily dose safety and tolerability data for TSC. We expect corresponding pharmacokinetic and other secondary endpoint data from this trial to be available early in the second quarter of 2021. Obtaining these data represents the first, major step in our ongoing efforts to implement our modified development strategy, intended to strategically gap-fill, supplement, and expand on our past development work in TSC, with the ultimate goal of maximizing the probability of regulatory approval and, if TSC is approved, commercial success.

During the next twelve months, we intend to continue to execute our strategy and accomplish the following principal, strategic objectives, all of which we expect to be able to fund with cash-on-hand:

- ***Complete the TSC Oxygenation Trials*** – As described in more detail under the heading — *Our Anticipated Next Steps in the TSC Development Program: The TSC Oxygenation Trials*, the next phase in our development plan is to evaluate TSC's effects in clinical models of oxygenation in an effort to establish a dose-response relationship. We expect to commence the TSC TCOM Trial before the end of March 2021 with data expected in the second quarter of 2021, and we intend to commence both the TSC DLCO Trial and TSC Induced Hypoxia Trial in the third quarter of 2021 with data expected from each study expected within two months of their respective completion.

- ***Initiate Phase 2 Trial of TSC in Hypoxia-related Indication*** – We believe positive data from one or more of the three TSC Oxygenation Trials would provide definitive evidence of TSC's enhancement of oxygenation, whether through increased uptake in the lungs, enhanced delivery, increased utilization at the tissue level, or some combination thereof. Positive data from any of these studies, if obtained, will guide the subsequent steps of our development strategy focused on demonstrating the clinical and therapeutic benefits of TSC in relevant patient populations on the hypoxia continuum. In particular, if successful in one or more of the three TSC Oxygenation Trials, we intend to initiate a Phase 2, controlled, clinical outcome study evaluating TSC in one or more appropriate hypoxia-related indications, which we refer to as our Planned Phase 2 Hypoxia-related Indication Trial, by the first quarter of 2022.

- ***Continue to Improve Our Efficiency and Effectiveness*** – This will include evaluating, refining, and improving our policies, procedures, and processes related to chemistry, manufacturing, and controls, quality assurance, information technology, intellectual property, human capital, and other areas, including as described in more detail under the headings, — *Products, Product Development, and Our Competition* and — *Our People and Human Capital Resources* in *Part I – Item 1. Business* of this Annual Report.

Our Anticipated Next Steps in the TSC Development Program: The TSC Oxygenation Trials

Following completion of the TSC COVID Trial in February 2021, the next step we have planned in the development of TSC is the design and execution of a trilogy of clinical studies using short-term, experimental models to evaluate the clinical effects of TSC on oxygenation. As of March 15, 2021, TSC has been administered to more than 180 subjects in our clinical trials. Data from these clinical trials have contributed significantly to our understanding of the safety, tolerability, and pharmacokinetics of TSC. In addition, post hoc analyses of two of our prior studies involving patients with peripheral artery disease with claudication and unresected GBM tumors have provided preliminary signals suggesting TSC's effect on oxygenation. However, neither of these studies was statistically powered to formally evaluate efficacy, and we therefore believe that further, robust clinical development of TSC requires a prospective exploration of the relationship between the level of exposure (dose) and response (change in oxygenation).

To this end, we plan to execute the three, short-term TSC Oxygenation Trials during 2021, each of which we expect to conduct in the U.S. and fund with cash-on-hand. We believe positive data from any or more of the three TSC Oxygenation Trials would provide evidence of a definitive effect of TSC on oxygenation, whether through increased uptake in the lungs, enhanced delivery, increased utilization at the tissue level, or some combination thereof. Positive data from any of these studies, if obtained, will also guide the subsequent steps of our development strategy focused on demonstrating the clinical and therapeutic benefits of TSC in relevant patient populations across the hypoxia continuum.

Assuming success in one or more of the three TSC Oxygenation Trials, we expect to identify and announce the specific, hypoxia-related indications we will target in advancing TSC's development in the fourth quarter of 2021 and intend to initiate our Planned Phase 2 Hypoxia-related Indication Trial in the first quarter of 2022.

Financial Summary

As of December 31, 2020, we had a cash and cash equivalents balance of $18.5 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 $14.2 million and $11.8 million for the years ended December 31, 2020 and 2019, 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, 2020, was $105.9 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 and planned TSC Oxygenation Trials and our Planned Phase 2 Hypoxia-related Indication Trial;
- any additional studies we may undertake, including other preclinical and clinical studies to support the filing of any NDA with the FDA;
- 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; 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, including the TSC TCOM Trial, the TSC VO2 Trial, and the TSC DLCO Trial. We expect that our existing cash and cash equivalents as of December 31, 2020, combined with the $36.7 million of aggregate gross proceeds received by the Company in connection with the completion of the February 2021 Offering (before deducting underwriting discounts and commissions and offering expenses payable by us) and the exercise of certain warrants to purchase common stock during the first quarter of 2021 prior to the date of this Annual Report, will enable us to fund our operating expenses and capital expenditure requirements, including expected costs related to the planned TSC Oxygenation Trials and our Planned Phase 2 Hypoxia-related Indication Trial 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.

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 (Expense)

We recognize income tax benefit to utilize indefinite deferred tax liabilities as a source of income against indefinite lived portions of our deferred tax assets. 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. These limitations may, in certain cases, limit the amount of income tax benefit that can be utilized annually to offset taxable income or tax liabilities in future periods. 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. In 2019, due to the significant changes to our stockholder base as a result of the equity financing we completed during that year, we performed an analysis under Section 382 of the Internal Revenue Code and, as a result, reduced the magnitude of our NOL carryforwards to account for the ownership changes. In addition, the cumulative benefit of our NOLs was remeasured, resulting in tax expense recognized during the year ended December 31, 2019. We have not yet performed an analysis to determine whether or not ownership changes that have occurred in year ended December 31, 2020 give rise to any further limitations.

Critical Accounting Policies

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 is 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, is uncertain, would take a number of years, and the costs would be significant. As the development efforts for DFN-529 continue, based on the facts and circumstances at the time of a future valuation for the purposes of assessing impairment, it is possible that the value for the IPR&D asset could be substantially reduced or eliminated, which could result in a maximum pre-tax charge to operations equal to the current carrying value of the asset, or $8.6 million as of December 31, 2020. We most recently tested the IPR&D intangible asset for impairment on October 1, 2020, which is our annual impairment testing date. In addition to our annual impairment testing, upon the occurrence of certain triggering events, we may determine that an interim IPR&D impairment analysis is warranted. There was no impairment to the IPR&D asset during the years ended December 31, 2020 and 2019.

Results of Operations for Year Ended December 31, 2020 Compared to Year Ended December 31, 2019

The following table summarizes our results of operations for the years ended December 31, 2020 and 2019:

	Year ended December 31,		
	2020	2019	Change
Operating expenses:			
Research and development	$ 9,427,667	$ 6,619,597	$ 2,808,070
General and administrative	6,444,109	4,834,284	1,609,825
Depreciation	103,168	97,915	5,253
Loss from operations	(15,974,944)	(11,551,796)	4,423,148
Interest income	114,257	85,302	28,955
Loss from operations before income taxes	(15,860,687)	(11,466,494)	(4,394,193)
Income tax benefit (expense)	1,675,381	(332,885)	2,008,266
Net loss	$ (14,185,306)	$ (11,799,379)	$ (2,385,927)

Research and development expenses were $9.4 million during the year ended December 31, 2020 compared to $6.6 million during the year ended December 31, 2019, an increase of 42.4%. A significant portion of this increase was attributable to the TSC COVID Trial, which was initiated in September 2020, and our related ramp-up, including a $1.1 million increase in manufacturing costs and a $2.2 million increase in clinical trial and other related R&D expenses. Other R&D costs, including share based compensation, also increased by $0.3 million. These increases were slightly offset by decreases of $0.3 million and $0.2 million related to the wind-down of our TSC GBM Trial and our TSC Stroke Trial, respectively and a decrease in salaries and wages expenses of $0.3 million.

General and administrative expenses were $6.4 million during the year ended December 31, 2020 compared to $4.8 million during the year ended December 31, 2019, an increase of 33.3%. The increase in G&A expense was primarily due to a $0.7 million increase in professional fees and a $0.9 million increase in salaries, wages, and stock-based compensation expense, including non-recurring expenses related to the retirement, resignation, and separation of our former Chief Executive Officer in the third quarter of 2020.

Interest income increased slightly for the year ended December 31, 2020 compared to the year ended December 31, 2019 on an absolute basis due to our having a larger cash and cash equivalents balance and therefore earning more interest during the year ended December 31, 2020 compared to the year ended December 31, 2019.

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 the our deferred tax assets. As a result of a deemed change in ownership under the provisions of Section 382 of the Tax Code, the cumulative benefit of our NOLs was remeasured during 2019 resulting in the reversal of an income tax benefit of $0.4 million recorded in 2018. Accordingly, net of a $0.1 million benefit related to losses incurred during the year, we recognized an income tax expense of $0.3 million for the year ended December 31, 2019.

Liquidity and Capital Resources

Working Capital

The following table summarizes our working capital as of December 31, 2020 and 2019:

	December 31,	
	2020	2019
Cash and cash equivalents	$ 18,515,595	$ 14,177,349
Prepaid expenses, deposits and other assets	260,825	472,464
Total current liabilities	2,435,783	1,721,421
Working capital	$ 16,340,637	$ 12,928,392

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, included the TSC Oxygenation Studies and our Planned Phase 2 Hypoxia-related Indication Trial, through 2023.

Cash Flows

The following table sets forth our cash flows for the years ended December 31, 2020 and 2019:

	December 31,	
Net cash (used in) provided by:	**2020**	**2019**
Operating activities	$ (13,552,628)	$ (9,858,375)
Financing activities	17,890,875	16,044,552
Net increase in cash and cash equivalents	$ 4,338,247	$ 6,186,177

Operating Activities

For the year ended December 31, 2020, net cash used in operating activities increased $3.7 million, or 37.5%, compared to the year ended December 31, 2019.

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.

Net cash used in operating activities of $9.9 million during the year ended December 31, 2019 was primarily attributable to our net loss of $11.8 million and a $0.3 million change in deferred income taxes. This amount was offset by our net change in operating assets and liabilities of $1.0 million, and non-cash charges comprised of $0.5 million of stock-based compensation expense and depreciation expense of $0.1 million.

Investing Activities

Cash flows from investing activities represent our sources and uses of cash from our investments, including purchases and sales of equipment and other assets. During each of the years ended December 31, 2020 and 2019, we had no such cash flows.

Financing Activities

For the year ended December 31, 2020, net cash provided by financing activities increased $1.8 million, or 11.5%, compared to the year ended December 31, 2019.

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.

Net cash provided by financing activities of $16.0 million during the during the year ended December 31, 2019 was primarily attributable to the $12.3 million in aggregate proceeds (net of underwriting discounts and commissions payable by us) received in connection with the May 2019 Offering, the November 2019 Offering, and the December 2019 Offering and $3.9 million in proceeds received in connection with the exercise of common stock warrants during the year. These cash inflows were offset in part by the payment of $0.2 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, DFN-529, and our other product candidates. As of the date of this Annual Report, most our cash resources for clinical development are dedicated to our ongoing and planned TSC Oxygenation Trials and our Planned Phase 2 Hypoxia-related Indication Trial. 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, 2020, 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, 2020 and 2019, 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, 2020 and 2019, 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 Matter

The critical audit matter communicated below is a matter arising from the current period audit of the consolidated financial statements that was communicated or required to be communicated to the audit committee and that: (1) relates to accounts or disclosures that are material to the consolidated financial statements and (2) involved our especially challenging, subjective, or complex judgments. The communication of a critical audit matter does not alter in any way our opinion on the consolidated financial statements, taken as a whole, and we are not, by communicating the critical audit matter below, providing a separate opinion on the critical audit matter or on the accounts or disclosures to which it relates.

Deemed dividend

As discussed in Note 7 to the consolidated financial statements, the Company entered into a warrant exercise agreement with an investor who held a previously outstanding warrant. The Company recognized a deemed dividend of $2.0 million to reflect the fair value of the consideration given as an inducement for the investor to exercise the warrants.

We identified the evaluation of the deemed dividend as a critical audit matter. A higher degree of auditor judgment was required to evaluate the application of the accounting guidance due to the unique nature of the transaction with the investor.

The following are the procedures we performed to address this critical audit matter. We read and evaluated the Company's accounting memorandum that documented the business purpose, the terms of the agreements underlying the transaction, and the factors the Company considered in determining the applicable accounting treatment. We compared the facts and circumstances in the Company's accounting memorandum to the agreements underlying the transaction.

/s/ KPMG LLP

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

McLean, Virginia
March 16, 2021

DIFFUSION PHARMACEUTICALS INC.

CONSOLIDATED BALANCE SHEETS

	December 31, 2020	December 31, 2019
Assets		
Current assets:		
Cash and cash equivalents	$ 18,515,595	$ 14,177,349
Prepaid expenses, deposits and other current assets	260,825	472,464
Total current assets	18,776,420	14,649,813
Property and equipment, net	149,198	252,366
Intangible asset	8,639,000	8,639,000
Right of use asset	149,162	247,043
Other assets	15,771	322,301
Total assets	$ 27,729,551	$ 24,110,523
Liabilities and Stockholders' Equity		
Current liabilities:		
Accounts payable	$ 545,844	$ 1,251,412
Accrued expenses and other current liabilities	1,776,470	358,532
Current operating lease liability	113,469	111,477
Total current liabilities	2,435,783	1,721,421
Deferred income taxes	443,893	2,119,274
Noncurrent operating lease liability	35,693	135,566
Total liabilities	2,915,369	3,976,261
Commitments and Contingencies (Note 6)		
Stockholders' Equity:		
Common stock, $0.001 par value: 1,000,000,000 shares authorized; 64,015,441 and 33,480,365 shares issued and outstanding at December 31, 2020 and 2019, respectively	64,016	33,481
Additional paid-in capital	130,659,550	111,824,859
Accumulated deficit	(105,909,384)	(91,724,078)
Total stockholders' equity	24,814,182	20,134,262
Total liabilities and stockholders' equity	$ 27,729,551	$ 24,110,523

See accompanying notes to consolidated financial statements.

DIFFUSION PHARMACEUTICALS INC.

CONSOLIDATED STATEMENTS OF OPERATIONS

	Year Ended December 31,	
	2020	**2019**
Operating expenses:		
Research and development	$ 9,427,667	$ 6,619,597
General and administrative	6,444,109	4,834,284
Depreciation	103,168	97,915
Loss from operations	(15,974,944)	(11,551,796)
Other income:		
Interest income	114,257	85,302
Loss from operations before income taxes	(15,860,687)	(11,466,494)
Income tax benefit (expense)	1,675,381	(332,885)
Net loss	$ (14,185,306)	$ (11,799,379)
Deemed dividend arising from warrant exchange	(1,950,378)	—
Net loss attributable to common stockholders	$ (16,135,684)	$ (11,799,379)
Share information:		
Net loss per share of common stock, basic and diluted	$ (0.30)	$ (1.76)
Weighted average shares outstanding, basic and diluted	53,831,973	6,706,509

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, 2018	3,376,230	$ 3,377	$ 95,532,881	$ (79,924,699)	$ 15,611,559
Issuance of common stock, pre-funded warrants and warrants, net of issuance costs	12,688,276	12,688	11,905,207	—	11,917,895
Issuance of common stock upon exercise of warrants	17,415,859	17,416	3,871,009	—	3,888,425
Stock-based compensation expense	—	—	515,762	—	515,762
Net loss	—	—	—	(11,799,379)	(11,799,379)
Balance at December 31, 2019	33,480,365	33,481	111,824,859	(91,724,078)	20,134,262
Issuance of common stock 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

See accompanying notes to consolidated financial statements.

DIFFUSION PHARMACEUTICALS INC.

CONSOLIDATED STATEMENTS OF CASH FLOWS

	Year Ended December 31,	
	2020	**2019**
Operating activities:		
Net loss	$ (14,185,306)	$ (11,799,379)
Adjustments to reconcile net loss to net cash used in operating activities:		
Depreciation	103,168	97,915
Stock-based compensation expense	736,119	515,762
Change in deferred income taxes	(1,675,381)	332,885
Changes in operating assets and liabilities:		
Prepaid expenses, deposits and other assets	518,169	426,774
Accounts payable, accrued expenses and other liabilities	950,602	567,668
Net cash used in operating activities	(13,552,629)	(9,858,375)
Cash flows provided by financing activities:		
Proceeds from the sale of common stock	10,827,100	—
Proceeds from the sale of common stock, pre-funded warrants and warrants	—	12,318,956
Proceeds from the exercise of common stock warrants and pre-funded warrants	8,046,103	3,888,425
Payment of offering costs	(982,328)	(162,829)
Net cash provided by financing activities	17,890,875	16,044,552
Net increase in cash and cash equivalents	4,338,247	6,186,177
Cash and cash equivalents at beginning of year	14,177,349	7,991,172
Cash and cash equivalents at end of year	$ 18,515,595	$ 14,177,349
Supplemental disclosure of non-cash investing and financing activities:		
Offering costs in accounts payable and accrued expenses	$ —	$ 238,232
Operating lease right of use asset and liability	$ —	$ 334,205

See accompanying notes to consolidated financial statements.

1. Organization and Description of Business

Diffusion Pharmaceuticals Inc., a Delaware corporation, an innovative biopharmaceutical company developing novel therapies that enhance the body's ability to deliver oxygen to the 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 addition to TSC, the Company's product candidate DFN-529, a novel, allosteric PI3K/Akt/mTOR pathway inhibitor, is in early-stage development. The Company previously completed two Phase 1 clinical trials evaluating DFN-529 in age-related macular degeneration. DFN-529 was also previously in preclinical development in oncology, specifically GBM.

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, 2020, combined with the proceeds received by the Company in connection with the completion of the February 2021 Offering and the exercise of certain warrants to purchase common stock during the first quarter of 2021 prior to the date of this Annual Report, will enable it to fund its operating expenses and capital expenditure requirements, including expected costs related to the planned TSC Oxygenation Trials and the Planned Phase 2 Hypoxia-related Indication Trial 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.

Long-Lived Assets

Long-lived assets are reviewed for potential impairment whenever events indicate that the carrying amount of such assets may not be recoverable. The Company does this by comparing the carrying value of the long-lived assets with the estimated future undiscounted cash flows expected to result from the use of the assets, including cash flows from disposition. If it is determined an impairment exists, the asset is written down to its estimated fair value. The Company has not recognized any impairment of long-lived assets during the years ended December 31, 2020 and 2019.

Intangible Asset

The Company has an indefinite-lived IPR&D asset, DFN-529, which has a balance of $8.6 million at both December 31, 2020 and December 31, 2019. DFN-529 is a PI3K/Akt/mTOR pathway inhibitor in preclinical development for oncology.

Intangible assets deemed to have indefinite lives are not amortized but rather are assessed for impairment annually on October 1 of the Company's fiscal year or more frequently if impairment indicators exist. There was no impairment to the Company's DFN-529 intangible asset recognized during the years ended December 31, 2020 and 2019.

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.

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 50.0% 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 their 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 life 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 attributable 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,	
	2020	2019
Common stock warrants	9,100,112	22,385,141
Stock options	2,240,204	309,276
	11,340,316	22,694,417

Recently Issued But Not Yet 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 is currently analyzing the impact of ASU No. 2019-12 on the consolidated financial statements.

Recently Adopted Accounting Pronouncements

In August 2018, the FASB issued ASU 2018-03, *Disclosure Framework- Changes to the Disclosure Requirements for Fair Value Measurements,* which changes the fair value measurement disclosure requirements of ASC 820. The goal of the ASU is to improve the effectiveness of ASC 820's disclosure requirements. The Company adopted this standard in January 2020 and the adoption did not have a material impact on its related disclosures.

4. Property and Equipment

Property and equipment consists of the following:

	December 31,	
	2020	2019
Laboratory equipment	$ 182,357	$ 182,357
Furniture and office equipment	151,442	151,442
Leasehold improvements	430,000	430,000
Total property and equipment	763,799	763,799
Less: accumulated depreciation and amortization	(614,601)	(511,433)
Property and equipment, net	$ 149,198	$ 252,366

Depreciation and amortization expense was approximately $0.1 million for both the years ended December 31, 2020 and 2019.

5. Accrued Expenses and Other Current Liabilities

Accrued expenses and other current liabilities consist of the following:

	December 31,	
	2020	2019
Accrued payroll and payroll related expenses	$ 653,899	$ 182,708
Accrued professional fees	31,809	48,338
Accrued clinical studies expenses	1,055,398	57,378
Other	35,364	70,108
Total	$ 1,776,470	$ 358,532

6. Commitments and Contingencies

Office Space Lease Commitment

The Company has a non-cancelable operating lease for office and laboratory space in Charlottesville, Virginia, which began in April 2017 and, as of December 31, 2020, has a remaining lease term of approximately 1.3 years. The discount rate used to account for the Company's operating lease is the Company's estimated incremental borrowing rate of 10.0%. The original term of the lease ends in the second quarter of 2022 and the Company has an option to extend for another 5 years. This option to extend was not recognized as part of the Company's measurement of the right-of-use asset and operating lease liability as of December 31, 2020.

Rent expense related to the Company's operating lease for both the years ended December 31, 2020 and 2019 was approximately $0.1 million. Future minimum rental payments under the Company's non-cancelable operating lease at December 31, 2020 were as follows:

	Rental Commitments
2021	$ 118,519
2022	39,735
Total	158,254
Less: imputed interest	(9,092)
	$ 149,162

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 its 401(k) Plan, which covers all employees who qualify under the terms of the plan. Eligible employees may elect to contribute to the 401(k) Plan up to 90.00% of their compensation, limited by the IRS-imposed maximum. The Company provides a safe harbor match with a maximum amount of 4.0% of the participant's compensation. The Company made matching contributions under the 401(k) Plan of approximately $56,000 and $68,000 for the years ended December 31, 2020 and 2019, 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 hearing for the petition and motion on April 14, 2015, the Court granted the Company's petition to compel arbitration and a motion to stay the action. On January 8, 2016, the plaintiff filed an arbitration demand with the American Arbitration Association. On November 19, 2018 at an Order to Show Cause Re Dismissal Hearing, the Court found sufficient grounds not to dismiss the case, and an arbitration hearing was scheduled for November 2020. In August 2020, due to the ongoing COVID-19 pandemic and related restrictions on gatherings in the State of California, the arbitration hearing was postponed to August 16, 2021. The Company believes this matter is without merit and intends to defend the arbitration vigorously. However, at this stage, the Company is unable to predict its outcome and the possible loss or range of loss, if any, associated with its resolution or any potential effect the matter may have on the Company's financial position. Depending on the outcome or resolution of this matter, it could have a material effect on the Company's financial position.

7. Stockholders' Equity and Common Stock Warrants

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 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(the Prior Warrant). In consideration for the exercise of the Prior Warrant for cash and an additional $0.125 per each share of common stock resulting from the exercise, 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. 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 is recorded in the Company's consolidated statement of operations during the year ended December 31, 2020 as an increase to the net loss attributable to common stockholders for purposes of computing net loss per share, basic and diluted.

In connection with the warrants exercised in May 2020, 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.

2019 Common Stock Offerings

In December 2019, Company completed the December 2019 Offering, an offering of 6,266,787 shares of its common stock and warrants to purchase 6,266,787 shares of common stock. The shares of common stock and warrants were sold for a combined purchase price of $0.5585 per share for net proceeds of $3.0 million. The December 2019 Offering warrants are exercisable beginning on the date of their issuance until June 13, 2025 at an initial exercise price equal to $0.4335 per share.

In addition, at the closing of the December 2019 Offering, the Company issued warrants to purchase up to 313,339 shares of common stock to designees of the placement agent. The placement agent's warrants have an exercise price of $0.6981 per share and a term of five years from the date of issuance.

In November 2019, the Company completed the November 2019 Offering, a registered direct public offering of 5,104,429 shares of its common stock, and 6,324,143 pre-funded warrants each to purchase one share of common stock, together with warrants to purchase up to 22,857,144 shares of common stock at a combined public offering price of $0.35 per share and associated warrants for total net proceeds of $3.3 million. The warrants were issued with an exercise price of $0.35 per warrant and are exercisable beginning on their date of issuance. Of the warrants issued, 11,428,572 have a term of 18 months and 11,428,572 have a term of 5 years. During the year ended December 31, 2019, 11,091,716 of those warrants were exercised for additional proceeds of $3.9 million.

In addition, at the closing of the November 2019 Offering, the Company issued warrants to purchase up to 571,429 shares of common stock to designees of the placement agent. The placement agent's warrants have an exercise price of $0.4375 per share and a term of five years from the date of issuance.

In May 2019, the Company completed the May 2019 Offering, a registered direct public offering of 1,317,060 shares of common stock and a private placement of warrants to purchase 1,317,060 shares of common stock. The shares of common stock and warrants were sold for a combined purchase price of $4.895 for total net proceeds of $5.6 million. The warrants are exercisable beginning on the date of their issuance until November 29, 2024 at an initial exercise price equal to $5.00.

In addition, at the closing of the May 2019 Offering, the Company issued warrants to purchase up to 65,853 shares of common stock to designees of the placement agent. The placement agent's warrants have an exercise price of $6.11875 per share, a term of 5 years from the date of issuance and otherwise substantially similar terms to the form of the investor warrant.

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, 2020, 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	497,140	$0.35 - $0.4375	May 2024
Common stock warrants issued related to the December 2019 Offering	313,339	$0.4335 - $0.6981	December 2024 and June 2025
Common stock warrants issued related to the May 2020 Offering	571,429	$1.31	March 2025
Common stock warrants issued related to the May 2020 Investor Warrant Exercise	4,250,000	$0.5263 - $0.5938	November 2025
	9,100,112		

During the year ended December 31, 2020, no warrants expired and 19,106,504 warrants were exercised for gross proceeds of $8.0 million. During the year ended December 31, 2019, 1,767 warrants expired and 17,415,859 warrants were exercised for net proceeds of $3.9 million.

8. 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, 2,560,618 shares were added to the reserve as of January 1, 2021, which 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, 2020, there were no shares of common stock available for future issuance under the 2015 Equity Plan. Further, the Company granted options to purchase 270,000 shares of common stock to employees during the year ended December 31, 2020 that were granted outside of the 2015 Equity Plan as an inducement material to the employee's acceptance of employment with the Company in accordance with Nasdaq Listing Rule 5635(c)(4). 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,	
	2020	2019
Research and development	$ 164,791	$ 54,155
General and administrative	571,328	461,607
Total stock-based compensation expense	$ 736,119	$ 515,762

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

	Number of Options	Weighted average exercise price per share	Weighted average remaining contractual life (in years)	Aggregate Intrinsic Value
Balance at January 1, 2019	203,736	$ 88.14		
Granted	117,270	2.62		
Forfeited	(11,583)	83.81		
Expired	(147)	276.00		
Balance at December 31, 2019	309,276	$ 55.78	6.98	—
Granted	1,931,100	0.68		
Expired	(172)	142.50		
Outstanding at December 31, 2020	2,240,204	$ 8.28	8.90	$ 289,067
Exercisable at December 31, 2020	1,129,733	$ 15.64	8.28	$ 219,010
Vested and expected to vest at December 31, 2020	2,240,204	$ 8.28	8.90	$ 289,067

The weighted average grant date fair value of stock option awards granted was $0.64 and $2.16 during the years ended December 31, 2020 and 2019, respectively. The total fair value of options vested during the years ended December 31, 2020 and 2019 were $0.7 million and $0.6 million, respectively. No options were exercised during any of the periods presented. At December 31, 2020, there was $0.8 million of unrecognized compensation cost related to unvested options that will be recognized as expense over a weighted-average period of 2.2 years.

The grant date fair value of employee stock options is determined using the Black-Scholes Model. The following assumptions were used during the years ended December 31, 2020 and 2019:

	2020	2019
Expected term (in years)	5.31 — 10.00	5.25 — 5.77
Risk-free interest rate	0.4% — 1.7%	1.9% — 2.5%
Expected volatility	113.4% — 124.8%	112.4% — 114.4%
Dividend yield	— — —	— — —

Restricted Stock Unit Awards

During the year ended December 31, 2020, the Company granted 153,000 restricted stock units to members of the board of directors of the Company. The weighted average grant date fair value of the restricted stock units granted during the year ended December 31, 2020 was $0.65. The shares begin to vest 18 months after the grant date. The Company recognized approximately $18,000 in expense related to these units during the year ended December 31, 2020. At December 31, 2020, there was approximately $82,000 of unrecognized compensation cost that will be recognized over a weighted average period of 2.4 years.

9. Income Taxes

Since inception, the Company has incurred net losses, and until 2018, had not recorded any U.S. federal or state income tax benefits for the losses. In 2018, as a result of the change in net operating loss carryforward period associated with the 2017 Tax Act, the Company recognized an income tax benefit to reflect the adjustment allowed by the 2017 Tax Act to utilize indefinite deferred tax liabilities as a source of income against indefinite lived portions of the Company's deferred tax assets. In 2019, as a result of a change in ownership under the provisions of Internal Revenue Code Section 382, the cumulative benefit of net operating losses was remeasured which resulted in tax expense to reverse the 2018 benefit recorded and record a benefit relative to losses incurred in 2019 after the date of the change in ownership.

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, 2020**	**December 31, 2019**
Net operating loss carryforwards	$ 3,864,189	$ 1,504,496
Stock-based compensation	1,571,227	1,381,750
Orphan Drug credits	541,384	81,700
Lease liability	38,394	63,589
Capitalized start-up costs and other	10,709,631	9,187,898
Valuation allowance	(14,906,646)	(12,051,440)
Deferred tax assets	1,818,179	167,993
Deferred tax liabilities		
Intangible assets	(2,223,678)	(2,223,678)
Right of use asset	(38,394)	(63,589)
Deferred tax liabilities	(2,262,072)	(2,287,267)
Net deferred tax liability	$ (443,893)	$ (2,119,274)

The Company does not have unrecognized tax benefits as of December 31, 2020 or December 31, 2019. 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, 2020 and 2019 of approximately:

Combined NOL Carryforwards:	December 31, 2020	December 31, 2019
Federal	$ 15,013,388	$ 5,844,972
State	15,007,966	5,844,972

The pre-2018 net operating loss carryforwards begin expiring in 2020 for both federal and state income tax purposes. In November 2019, as a result of a change of ownership, under the provisions of Internal Revenue Code Section 382 and similar state provisions, the Company's ability to utilize their net operating loss carryforwards to offset future income was limited. The Company recorded a valuation allowance against a portion of their deferred tax assets as of December 31, 2020 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, 2020	December 31, 2019
Federal tax benefit at statutory rate	(21.0)%	(21.0)%
State tax, net of Federal benefit	(4.7)%	(2.5)%
Orphan drug credit	(2.9)%	25.3 %
Change in valuation allowance	18.1 %	(7.5)%
Stock compensation	— %	8.6 %
Other	— %	0.1 %
Total provision	(10.5)%	3.0 %

The Company files income tax returns in the U.S. federal jurisdiction and various state jurisdictions. The Company's 2017 to 2019 tax years remain open and subject to examination.

10. Related Party Transactions

The Company's Director of Information Technologies is the son of the Chairman of the Board of Directors and he has held that position since December 2014.

11. Subsequent Events

2021 Warrant Exercises

From January 1, 2021 through March 15, 2021, warrants were exercised by multiple holders to purchase a total of 4,230,000 shares of the Company's common stock for aggregate gross proceeds of approximately $2.2 million.

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 $31.2 million, after deducting underwriting commissions, discounts, and expenses but prior to deducting other offering costs. 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.

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 Senior Vice President, Finance, our management conducted an evaluation of the effectiveness of our internal control over financial reporting based on the framework in *Internal Control—Integrated Framework (2013)* issued by the Committee of Sponsoring Organizations of the Treadway Commission. Based on that evaluation, our management concluded that our internal control over financial reporting was effective as of December 31, 2020.

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, 2020 that has materially affected, or is reasonably likely to materially affect, our internal control over financial reporting.

ITEM 9B. OTHER INFORMATION

None.

PART III

ITEM 10. DIRECTORS, EXECUTIVE OFFICERS AND CORPORATE GOVERNANCE

The information required by Item 10 of Form 10-K will be set forth in the Proxy Statement and is incorporated herein by reference.

ITEM 11. EXECUTIVE COMPENSATION

The information required by Item 11 of Form 10-K will be set forth in the Proxy Statement and is incorporated herein by reference.

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

The information required by Item 12 of Form 10-K will be set forth in the Proxy Statement and is incorporated herein by reference.

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

The information required by Item 13 of Form 10-K will be set forth in the Proxy Statement and is incorporated herein by reference.

ITEM 14. PRINCIPAL ACCOUNTING FEES AND SERVICES

The information required by Item 14 of Form 10-K will be set forth in the Proxy Statement and is incorporated herein by reference.

PART IV

ITEM 15. EXHIBITS, FINANCIAL STATEMENT SCHEDULES

1. Our financial statements are included in *Part II – Item 8. Financial Statements and Supplementary Data* 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. Financial Statements and Supplementary Data* of this Annual Report.

3. The exhibits set forth in the following "Index to Exhibits" are filed with, furnished with, and/or incorporated herein by reference, as described thereon. 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., 1317 Carlton Avenue, Suite 200, 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	Employment Agreement, dated as of September 6, 2016, by and between David G. Kalergis and Diffusion Pharmaceuticals Inc.*	Incorporated by reference to Exhibit 10.1 to the registrant's current report on Form 8-K filed on September 8, 2016
10.6	Separation Agreement dated as of September 8, 2020 by and between David G. Kalergis and Diffusion Pharmaceuticals Inc.*	Incorporated by reference to Exhibit 10.1 to the registrant's current report on Form 8-K filed on September 9, 2020
10.7	Employment Agreement, dated as of October 18, 2016, by and between John L. Gainer and Diffusion Pharmaceuticals Inc.*	Incorporated by reference to Exhibit 10.18 to the registrant's annual report on Form 10-K/A filed on April 28, 2017
10.8	Separation Agreement, dated as of March 12, 2020, by and between John L. Gainer and Diffusion Pharmaceuticals Inc.*	Incorporated by reference to Exhibit 10.1 to the registrant's current report on Form 8-K filed on March 18, 2020
10.9	Consulting Agreement, dated as of March 12, 2020, by and between John L. Gainer and Diffusion Pharmaceuticals Inc.*	Incorporated by reference to Exhibit 10.2 to the registrant's current report on Form 8-K filed on March 18, 2020
10.1	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
10.11	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
10.12	Form of Stock Option Award Agreement*	Incorporated by reference to Exhibit 10.5 to the registrant's annual report on Form 10-K for the year ended December 31, 2017
10.13	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
10.14	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
10.15	Form of Securities Purchase Agreement, dated as of May 18, 2020, by and among Diffusion Pharmaceuticals Inc. and the purchasers party thereto	Incorporated by reference to Exhibit 10.1 to the registrant's current report on Form 8-K filed on May 20, 2020
10.16	Lease Agreement, dated March 31, 2017, by and between Diffusion Pharmaceuticals Inc. and One Carlton LLC	Incorporated by reference to Exhibit 10.1 to the registrant's current report on Form 8-K filed on March 15, 2017
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, 2020, formatted in XBRL (Extensible Business Reporting Language): (i) Consolidated Balance Sheets, (ii) Consolidated Statements of Operations, (iii) Consolidated Statements of Cash Flows, and (iv) Notes to Consolidated Financial Statements	Filed herewith

* 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 16, 2021

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 16, 2021
/s/ William K. Hornung William K. Hornung	Chief Financial Officer (Principal Financial and Accounting Officer)	March 16, 2021
/s/ David G. Kalergis David G. Kalergis	Chairman of the Board	March 16, 2021
/s/ Robert Adams Robert Adams	Director	March 16, 2021
/s/ Jane Hollingsworth Jane Hollingsworth	Director	March 16, 2021
/s/ John L. Gainer, Ph.D. John L. Gainer, Ph.D.	Director	March 16, 2021
/s/ Mark T. Giles Mark T. Giles	Director	March 16, 2021
/s/ Alan Levin Alan Levin	Director	March 16, 2021

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

The Board of Directors
Diffusion Pharmaceuticals Inc.:

We consent to the incorporation by reference in the registration statements (No. 333-206408, No. 333-206409, No. 333-218060, No. 333-226782, No. 333-233381, and No. 333-238233) 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 Diffusion Pharmaceuticals Inc. of our report dated March 16, 2021, with respect to the consolidated balance sheets of Diffusion Pharmaceuticals Inc. as of December 31, 2020 and 2019, and the related consolidated statements of operations, changes in stockholders' equity, and cash flows for each of the years then ended, and the related notes, which report appears in the December 31, 2020 annual report on Form 10-K of Diffusion Pharmaceuticals Inc.

/s/ KPMG LLP

McLean, Virginia
March 16, 2021

Exhibit 31.1

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

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

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

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

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

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

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

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

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

Date: March 16, 2021

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

Exhibit 31.2

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

I, William K. Hornung, certify that:

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

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

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

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

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

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

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

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

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

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

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

Date: March 16, 2021

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

Exhibit 32.1

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

In connection with the Annual Report on Form 10-K of Diffusion Pharmaceuticals Inc. (the "Company") for the period ended December 31, 2020 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.

Date: March 16, 2021

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

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