UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

FORM 8-K
CURRENT REPORT
Pursuant to Section 13 or 15(d) of
the Securities Exchange Act of 1934

Date of Report (Date of earliest event reported): September 9, 2021

DIFFUSION PHARMACEUTICALS INC.
(Exact name of registrant as specified in its charter)

Delaware	**000-24477**	**30-0645032**
(State or other jurisdiction of incorporation)	(Commission File Number)	(I.R.S. Employer Identification No.)

1317 Carlton Avenue, Suite 200 **Charlottesville, Virginia** (Address of principal executive offices)	**22902** (Zip Code)

(434) 220-0718
(Registrant's telephone number, including area code)

Not applicable
(Former name or former address, if changed since last report)

Check the appropriate box below if the Form 8-K filing is intended to simultaneously satisfy the filing obligation of the registrant under any of the following provisions:

☐ Written communications pursuant to Rule 425 under the Securities Act (17 CFR 230.425)

☐ Soliciting material pursuant to Rule 14a-12 under the Exchange Act (17 CFR 240.14a-12)

☐ Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act (17 CFR 240.14d-2(b))

☐ Pre-commencement communications pursuant to Rule 13e-4(c) under the Exchange Act (17 CFR 240.13e-4(c))

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

Title of each class	Trading Symbol(s)	Name of each exchange on which registered
Common Stock, par value $0.001 per share	DFFN	NASDAQ Capital Market

Indicate by check mark whether the registrant is an emerging growth company as defined in Rule 405 of the Securities Act of 1933 (§ 230.405 of this chapter) or Rule 12b-2 of the Securities Exchange Act of 1934 (§ 240.12b-2 of this chapter).

Emerging growth company ☐

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

Item 7.01 Regulation FD Disclosure

Certain information concerning the business, clinical studies, development plans, and financial position of Diffusion Pharmaceuticals Inc. (the "Company" or "we") that we expect to use at certain conferences, meetings, and presentations is available on our website, www.diffusionpharma.com, under "Investors – Presentations." Representatives of the Company may use this presentation, in whole or in part, and possibly with non-material modifications, periodically in connection with conferences, meetings, and presentations to investors, analysts and others.

The information contained in the presentation is summary information that is intended to be considered in the context of the Company's filings with the Securities and Exchange Commission ("SEC") and other public announcements that we may make, by press release or otherwise, from time to time. The Company undertakes no duty or obligation to publicly update or revise the information contained in the presentation except as required by applicable law, although the Company may do so from time to time as its management believes is warranted. Any such updating may be made through the filing of other reports or documents with the SEC, through press releases, or through other public disclosure.

The Company makes no admission or representation as to the materiality of any information in the presentation or otherwise related thereto and contained in this Current Report on Form 8-K. Such information is furnished pursuant to Item 7.01 of Form 8-K and shall not be deemed to be "filed" for the purposes of Section 18 of the Securities Exchange Act of 1934, as amended (the "Exchange Act"), or otherwise subject to the liabilities of Section 18 of the Exchange Act unless we specifically incorporate it by reference in a document filed under the Exchange Act, nor shall it be deemed incorporated by reference in any filing under the Securities Act of 1933, as amended, except as previously set forth by specific reference in such a filing.

Item 8.01 Other Events

On September 9, 2021, the Company issued a letter to shareholders providing an update on recent events and outlook for the remainder of 2021 and early 2022. A copy of the letter is attached hereto as Exhibit 99.1 and is incorporated herein by reference.

Item 9.01 – Financial Statements and Exhibits

(d) Exhibits

Exhibit Number	**Description**
99.1	Letter to Shareholders, dated September 9, 2021
104	Cover Page Interactive Data File (embedded within the Inline XBRL document)

SIGNATURES

Pursuant to the requirements 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 hereunto duly authorized.

Dated: September 13, 2021

DIFFUSION PHARMACEUTICALS INC.

By: /s/ William Elder

Name: William Elder

Title: General Counsel

Diffusion Pharmaceuticals Issues Letter to Shareholders

CHARLOTTESVILLE, Va., September 9, 2021 -- **Diffusion Pharmaceuticals Inc. (NASDAQ: DFFN)** ("Diffusion" or the "Company"), an innovative biopharmaceutical company developing novel therapies that enhance the body's ability to deliver oxygen to areas where it is needed most, today announced that Robert Cobuzzi, Jr., Ph.D., Chief Executive Officer, has issued a Letter to Shareholders. The letter provides an update on recent events and outlook for the remainder of 2021 and early 2022.

The full text of the letter follows:

Diffusion Pharmaceuticals Shareholder Letter

September 9, 2021

Dear Fellow Stockholders,

I assumed the role of President and CEO at Diffusion Pharmaceuticals one year ago, in September 2020. Since that time, we have made many organizational and strategic advances and have endeavored to regularly communicate our progress. The purpose of this letter is to summarize these changes, highlight the data obtained from our clinical trials and describe how we plan to use the data to direct our development strategy for our lead product candidate, trans sodium crocetinate (TSC).

Over the coming weeks and months, we will continue to communicate our plans and progress through our usual channels, including press releases, investor conference presentations, media interviews and SEC filings. We also will seek to expand the depth and breadth of information available about our development activities through a series of podcasts featuring our Chief Medical Officer, Chris Galloway, M.D and me. The first episode of this podcast series, entitled "The Science of Solving for Hypoxia" is available through the Diffusion website at www.diffusionpharma.com.

1. *Organizational Changes*

The story of every organization is primarily about its people, so let's start there.

Since last September, there has been significant change at every level of our organization, from the Board of Directors (Board) to the management team and to our operating team. We have implemented these changes to most effectively position us for short and longer term success.

I joined the Diffusion Board in January 2020 and was appointed CEO in September 2020. My scientific training and expertise, coupled with my significant biopharmaceutical industry experience in drug development and business development, match well with the current needs of Diffusion. Bill Hornung, our Chief Financial Officer since late 2018, is another industry veteran. Bill has been a great partner to me, both to provide historical context and in helping to shape Diffusion for the future. Last fall we further enhanced our management team with the addition of two very skilled leaders: our General Counsel, Bill Elder, and our Chief Medical Officer, Dr. Chris Galloway.

In addition to management team talent, we also have added accomplished individuals throughout the organization, including in our administration, clinical operations, finance, quality assurance, and chemistry, manufacturing and controls (CMC) functions. As we move forward, we plan to continue to grow and supplement our team as Diffusion continues to mature.

At the Board level, Jane Hollingsworth, who joined the Board in August 2020, was appointed our new Board Chair in June 2021, bringing more than 25 years of experience founding and leading life sciences companies. Diana Lanchoney, M.D., and Eric Francois – both elected to the Board in June 2021 – bring extensive technical expertise and many years of biopharmaceutical company leadership experience to the Board. Jane, Diana and Eric add meaningful new perspectives to our Board, enhancing the skills available to support the organization.

Collectively, these changes already have had a meaningful, positive impact on our ability to refine and execute our strategy, which I believe position us well for future success.

2. *Development Strategy Changes*

Let’s talk more about the changes to our development strategy over the last 12 months.

Since the founding of Diffusion, the focus has been on developing TSC as a platform therapeutic that can be used to enhance standard-of-care treatment for conditions complicated by hypoxia. Today, the development of TSC remains the cornerstone of our strategy.

Over time, we have generated a substantial amount of data on TSC. This includes data on CMC, preclinical safety and efficacy data in a wide array of experimental models, clinical data on single dose safety, tolerability, and pharmacokinetics in healthy volunteers, and clinical safety and efficacy data evaluating TSC as an adjuvant therapy in the treatment of a variety of indications, as noted below.

- GBM and Stroke Data

In late 2017, a Phase 2/3 follow-on study in GBM patients initiated, and in late 2019 a Phase 2 clinical study in acute stroke patients was initiated. However, both of these studies were terminated prior to completion due to non-clinical factors, including a lack of adequate financial resources and, in the case of the stroke study, the onset of the COVID-19 pandemic in early 2020.

- COVID-19 Data

In April 2020, due to the anticipated persistence of the COVID-19 pandemic coupled with the strong belief in the potential of TSC to improve low tissue oxygen levels, we announced a clinical research program evaluating TSC in patients with COVID-19. This program led to our recently completed Phase 1b clinical study evaluating TSC in COVID-19 patients.

The 24 patient, Phase 1b COVID-19 trial was completed in February 2021. This study evaluated the safety and pharmacokinetics of ascending doses of TSC administered every six hours for at least five and up to 15 days, which was a more frequent dosing regimen than had been used in previous clinical studies. Topline results from primary endpoint data, announced shortly after study completion in February 2021, indicated TSC was safe and well-tolerated when administered using the more frequent dosing regimen. Secondary and exploratory endpoint data, announced in May 2021, indicated that patients receiving the highest TSC dose tested, 1.5 mg/kg, had (i) faster time to improvement in World Health Organization ordinal scale by day 7 and through day 29, (ii) reduced time on oxygen supplementation, and (iii) reduced hospital length of stay compared to those receiving lower doses.

It is important to recall that the COVID-19 trial was designed as a safety and tolerability study only and was not designed or powered to evaluate TSC's efficacy as a treatment for COVID-19.

Focused new development strategy

Last fall, we took the opportunity to conduct a thorough analysis of all available data to map a strategy for future success. The available data at that point supported TSC's potential to enhance the standard-of-care for many hypoxia-related indications but did not yet provide direct evidence of TSC's ability to enhance oxygenation in humans nor did it yet demonstrate the safest and most effective doses to produce this oxygenation effect.

In order to address these outstanding questions, in November 2020 we announced our plan to conduct a trilogy of short-term, clinical studies – collectively referred to as the Oxygenation Trials – utilizing three different experimental clinical models of oxygenation:

- The TCOM Trial was the first of our three Oxygenation Trials. In short, it was designed to measure the direct effects of TSC on peripheral tissue oxygenation (tcpO2) in healthy normal volunteers using a device called a transcutaneous oximeter (TCOM) that measures the release of oxygen from blood vessels through the skin. This study was completed in March 2021 and is described in more detail below.

- The Altitude Trial, which we expect to initiate in the fourth quarter of this year, is designed to measure the effects of TSC on maximal oxygen consumption and partial pressure of blood oxygen in healthy normal volunteers exercising under conditions that simulate altitude and induce hypoxia.

- The ILD-DLCO Trial, which we expect to initiate in the late fourth quarter of this year, is designed to measure the effects of TSC on the diffusion of carbon monoxide through the lungs (DLCO) 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, in patients previously diagnosed with interstitial lung disease (ILD).

The TCOM Study

The topline results of the TCOM study were announced in the second quarter of 2021. In this study, TSC was observed to be safe and well-tolerated at all doses tested with no serious adverse events or dose-limiting toxicities. Analysis of the primary endpoint data indicated a positive dose-response trend in TCOM readings with TSC as compared to placebo that persisted through the measurement period. Due in part to the small number of subjects in each cohort, and the inherent variability of tcpO2 measurement, the magnitude of effect was not statistically significant; however, the trends in the primary endpoint data indicated an improvement in peripheral oxygenation with TSC with no evidence of hyperoxygenation, a potentially toxic condition.

The figure below was created by subtracting the median response observed in the TCOM Trial's placebo group from the median response observed in each TSC dosage group at each of the measurement times during the one-hour period following dosing. As you can see, these data show increasing peripheral tissue oxygenation following TSC administration that persisted through the one-hour measurement period, particularly at the two highest doses tested (2.0 mg/kg and 2.5 mg/kg).

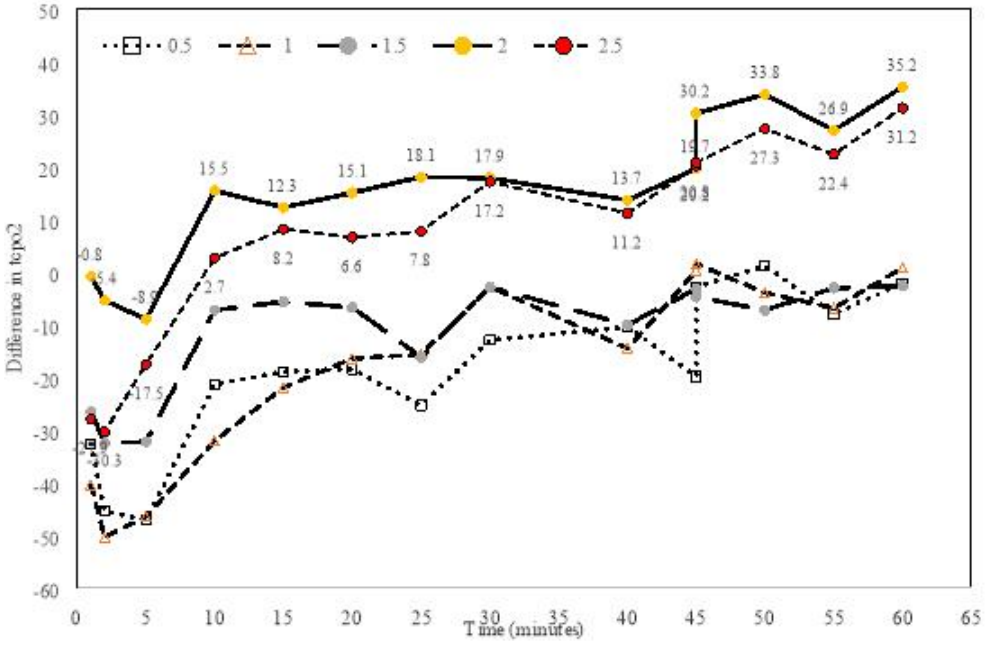

Figure 1. Effects of TSC on transcutaneous oxygen pressure (tcpO2). The graph was created by subtracting the median placebo response from the dose and time matched median TSC response.

We believe the TCOM Trial provides clinical evidence of exactly the outcomes we were hoping to see - that TSC facilitates the passive diffusion of oxygen from areas of high concentration to areas of low concentration without causing hyperoxygenation.

While the results of the TCOM study were not statistically significant - due we believe to the small sample size and the innovative trial design - they represent a positive and meaningful step towards the accomplishment of the strategic objectives of our Oxygenation Trials. Moreover, the 2.0 mg/kg and 2.5 mg/kg doses at which the effects of TSC were observed in the TCOM study are higher than the doses tested in any of the recent clinical trials of TSC. Therefore, in addition to providing evidence of a direct effect of TSC on oxygenation, these results help inform dose selection for future trials.

3. Looking Ahead

The body of data we have amassed to date makes us optimistic about the broad therapeutic potential of TSC. We believe the two remaining Oxygenation Trials – our Altitude and ILD-DLCO Trials – will answer additional outstanding questions, providing important additional data related to TSC dose and oxygenation as well as the mechanism of action. This information will guide our selection of the initial TSC indication to be studied for regulatory approval, which we expect to announce in the fourth quarter of this year.

Perhaps equally important to the progress we have made in our clinical program, as of June 30, 2021, we believe we have sufficient cash resources to fund our planned clinical trials and other operational needs through 2023. This includes the capacity to fully fund a Phase 2b clinical study evaluating TSC in the initial indication we will choose and identify in the fourth quarter of 2021 and expect to commence in the first half of 2022.

Looking forward, our team is committed to maximum effort, good planning, and strong execution as we strive to realize the potential of TSC for patients and for you, our stockholders. We are excited about Diffusion's prospects for the future and remain focused on executing the plan we have designed to develop TSC. We will continue to endeavor to win your confidence, successfully demonstrate the clinical value of TSC, and build a foundation for the future growth of Diffusion.

On behalf of the entire Diffusion team, I thank you for your continued support.

Best wishes for your health and safety,

Robert J. Cobuzzi Jr., Ph.D.
President and CEO
Diffusion Pharmaceuticals Inc.

About Diffusion Pharmaceuticals Inc.
Diffusion Pharmaceuticals Inc. is an innovative biopharmaceutical company developing novel therapies that enhance the body's ability to deliver oxygen to areas where it is needed most. Diffusion'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, Diffusion's product candidate DFN-529, a novel, allosteric PI3K/Akt/mTOR Pathway inhibitor, is in early-stage development. For more information, please visit us at www.diffusionpharma.com.

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Pharmaceuticals Inc.

Forward-Looking Statements
This press release includes express and implied forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995, as amended, including regarding the Company's near-term strategic priorities and the potential therapeutic value of TSC. The Company 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. Although the Company believes that it has a reasonable basis for each forward-looking statement contained herein, forward-looking statements by their nature involve risks and uncertainties, known and unknown, many of which are beyond the Company's control, and as a result, the Company's actual results could differ materially from those expressed or implied in any forward-looking statement. Particular risk and uncertainties include, among other things, those related to: the Company's ability to design, initiate, enroll, execute, and complete its ongoing and planned studies evaluating TSC; the optimal doses and dosing regimens of TSC in connection with the potential treatment of any particular disease or indication; general economic, political, business, industry, and market conditions, including the ongoing COVID-19 pandemic; and the other factors discussed under the heading "Risk Factors" in the Company's filings most recent Annual Report on Form 10-K and other filings with the U.S. Securities and Exchange Commission. Any forward-looking statements in this press release speak only as of the date hereof (or such earlier date as may be identified) and, except as required by applicable law, rule, or regulation, the Company undertakes no obligation to update any such statements after the date hereof.

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