# Section 1: 8-K (FORM 8-K)

## 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): December 27, 2017**

# 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 400**<br>**Charlottesville, Virginia**<br>(Address of principal executive offices) | **22902**<br>(Zip Code) |
|---|---|

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

**N/A**
(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))

**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 8.01. Other Events.**

On December 27, 2017, Diffusion Pharmaceuticals Inc. issued a press release announcing that its Phase 3 clinical trial using its lead small molecule trans sodium crocetinate in patients with newly-diagnosed inoperable glioblastoma multiforme brain cancer is now open for enrollment. A copy of the press release is attached hereto as Exhibit 99.1 and incorporated herein by reference.

**Item 9.01 Financial Statements and Exhibits.**

(d) Exhibits.

| Exhibit Number | Description |
|---|---|
| 99.1 | Press Release dated December 27, 2017 |

**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: December 29, 2017

**DIFFUSION PHARMACEUTICALS INC.**

By: /s/ David G. Kalergis
Name: David G. Kalergis
Title: Chief Executive Officer

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# Section 2: EX-99.1 (EXHIBIT 99.1)

**Exhibit 99.1**

Diffusio$_2$n Pharmaceuticals Inc.

## Diffusion Pharmaceuticals Begins Phase 3 Clinical Trial with TSC in Glioblastoma Multiforme

*Trial in newly diagnosed inoperable patients now open for enrollment*

**CHARLOTTESVILLE, Va. (December 27, 2017)** – **Diffusion Pharmaceuticals Inc. (NASDAQ: DFFN)** ("Diffusion" or "the Company"), a clinical-stage biotechnology company focused on extending the life expectancy of cancer patients, today announced that a Phase 3 clinical trial using its lead small molecule trans sodium crocetinate ("TSC") in patients with newly-diagnosed inoperable glioblastoma multiforme ("GBM") brain cancer, is now open for enrollment. The trial, which has been named INTACT (**IN**vestigating **T**sc **A**gainst **C**ancerous **T**umors), follows a previous Phase 2 GBM study in which the inoperable patient subgroup showed a nearly four-fold increase in survival compared with historical controls when TSC was added to their treatment regimen (40% alive at two years vs. 10.4%). TSC's innovative mechanism of action affects the tumor micro-environment, making treatment-resistant cancer cells more susceptible to the tumor-killing power of conventional radiation therapy ("RT") and chemotherapy (temozolomide) by re-oxygenation of the hypoxic portion of the tumor. The Company believes that a largely intact GBM tumor vasculature with limited surgical resection is conducive to TSC's tumor re-oxygenation properties, and that this contributed to the survival increase in the Phase 2 GBM inoperable patient subgroup.

The trial will screen 300 patients and enroll 264 in an effort to ensure that results from 236 patients will be available for analysis. Enrolled patients will be randomized in a 1:1 ratio into treatment and control groups. Patients in the treatment group will receive standard of care ("SOC") temozolomide and RT plus an intravenous bolus of TSC administered shortly before their SOC treatments. Patients in the control group will receive SOC alone. The study will compare overall survival at two years between patients in the two groups. Up to 100 clinical sites in the U.S. and Europe are expected to participate. The Company projects that enrollment will be completed by early 2019, with interim safety and efficacy data possible in 2020 and trial completion in 2021. Further site initiation is on-going, with first patient enrollment targeted for January 2018.

"Given the dire prognosis of inoperable GBM brain cancer, we are especially gratified to have the INTACT clinical trial open for enrollment. We believe that TSC can provide new hope for these patients, whose treatment options are so limited," said David Kalergis, Chief Executive Officer of Diffusion Pharmaceuticals. "The four-fold increase in inoperable GBM patients alive at two years in our Phase 2 trial is a particularly strong efficacy signal, and informs the design of our Phase 3 trial."

**About the GBM Phase 3 INTACT Trial**

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

TSC will be administered during both the RT and post-radiation temozolomide treatment periods to those subjects so randomized.

During the RT treatment period subjects will receive:

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

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

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

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

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

Further details about the trial protocol will be available shortly at www.clinicaltrials.gov.

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

The study will achieve the designed 80% statistical power at 198 events, where an event is defined as death. The first analysis will occur at the earlier of two years follow-up for all subjects or 198 events. If the first analysis is at 198 events, the analysis will be a standard 2-sided stratified log-rank test at the $\alpha$=0.05 significance level. If the first analysis is at two years, the Company will perform the analysis using the O'Brien-Fleming Method.

**About Treatment-Resistant Cancers and TSC**

Oxygen deprivation at the cellular level (hypoxia) is the result of rapid tumor growth, causing the tumor to outgrow its blood supply. Cancerous tumor cells thrive with hypoxia and the resultant changes in the tumor microenvironment cause the tumor to become resistant to RT and chemotherapy. Using a novel, proprietary mechanism of action, Diffusion's lead drug TSC appears to counteract tumor hypoxia – and therefore treatment resistance – by safely re-oxygenating tumor tissue, thus enhancing tumor kill and potentially prolonging patient life expectancy. Oxygen levels of normal tissue appear to remain unaffected upon administration of TSC.

**About Diffusion Pharmaceuticals Inc.**

Diffusion Pharmaceuticals Inc. is a clinical-stage biotechnology company focused on extending the life expectancy of cancer patients by improving the effectiveness of current standard-of-care (SOC) treatments including radiation therapy and chemotherapy. Diffusion is developing its lead product candidate, trans sodium crocetinate (TSC), for use in cancers where tumor hypoxia (oxygen deprivation) diminishes the effectiveness of SOC treatments. TSC targets the cancer's hypoxic micro-environment, re-oxygenating treatment-resistant tissue and making the cancer cells more vulnerable to the therapeutic effects of SOC treatments without the apparent addition of any serious side effects.

A Phase 3 randomized, controlled registration trial with TSC and SOC chemotherapy and radiation compared with SOC alone in 236 newly diagnosed and inoperable glioblastoma multiforme patients, is now open for enrollment. The trial, which has been named INTACT (**IN**vestigating **T**sc **A**gainst **C**ancerous **T**umors), was preceded by a Phase 2 clinical program completed in the fourth quarter of 2015 that evaluated 59 patients with newly-diagnosed glioblastoma multiforme, a type of brain cancer. This open-label, historically controlled study demonstrated a favorable safety and efficacy profile for TSC combined with SOC, including a 36% improvement in overall survival compared with the control group at two years. A strong efficacy signal was seen in the subset of inoperable patients where survival of TSC-treated patients at two years was nearly four-fold higher compared with the controls.

Due to its novel mechanism of action, TSC has safely re-oxygenated a range of tumor types in preclinical and clinical studies. Diffusion believes its therapeutic potential is not limited to one specific tumor type, thereby making it potentially useful to improve SOC treatments of other life-threatening cancers. Given TSC's safety profile and animal data, Diffusion believes that, with appropriate funding support, it can move directly into Phase 2 studies in other cancers. The Company also believes that TSC has potential application in other indications involving hypoxia, such as neurodegenerative diseases and emergency medicine. For example, a stroke program is now under discussion with doctors from the University of California in Los Angeles, the University of Southern California, and the University of Virginia, with whom Diffusion has established a joint team developing a program to test TSC, with an in-ambulance trial of TSC in ischemic and hemorrhagic stroke under consideration. Planning for such a trial is ongoing.

**Forward-Looking Statements**

To the extent any statements made in this news release deal with information that is not historical, these are forward-looking statements under the Private Securities Litigation Reform Act of 1995. Such statements include, but are not limited to, statements about the company's plans, objectives, expectations and intentions with respect to future operations and products, the potential of the company's technology and product candidates, the anticipated timing of future clinical trials and protocol review, and other statements that are not historical in nature, particularly those that utilize terminology such as "would," "will," "plans," "possibility," "potential," "future," "expects," "anticipates," "believes," "intends," "continue," "expects," other words of similar meaning, derivations of such words and the use of future dates. Forward-looking statements by their nature address matters that are, to different degrees, uncertain. Uncertainties and risks may cause the company's actual results to be materially different than those expressed in or implied by such forward-looking statements. Particular uncertainties and risks include: general business and economic conditions; the timing, success and results of the INTACT trial; the company's need for and ability to obtain additional financing; and the difficulty of developing pharmaceutical products, obtaining regulatory and other approvals and achieving market acceptance, and the various risk factors (many of which are beyond Diffusion's control) as described under the heading "Risk Factors" in Diffusion's filings with the United States Securities and Exchange Commission. All forward-looking statements in this news release speak only as of the date of this news release and are based on management's current beliefs and expectations. Diffusion undertakes no obligation to update or revise any forward-looking statement, whether as a result of new information, future events or otherwise.

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