May 5, 2020

Dear Diffusion Shareholders,

Diffusion Pharmaceuticals Inc., advanced on many fronts in 2019, with a focus on our stroke and cancer clinical trials and on intellectual property protection; however, the Company’s attention is now focused on developing our lead drug trans sodium crocetinate (TSC) as a possible treatment for COVID-19’s deadly effects. Because of the emergent nature of the pandemic, this letter will first describe the Company’s response to COVID-19 and then highlight the events of 2019.

COVID-19

On April 1, 2020, Diffusion announced that it began a cooperative research effort with the University of Virginia Health System (UVA) to evaluate TSC in patients with Acute Respiratory Distress Syndrome (ARDS) associated with COVID-19 infection. Patients with COVID-19 infections are at risk for developing ARDS, which can lead to death from systemic hypoxemia (general lack of oxygen to body tissue and vital organs).

On April 27, 2020, the Company announced the pre-IND submission to the U.S. Food and Drug Administration (FDA) of its planned clinical program using TSC in COVID-19 patients displaying severe respiratory symptoms and low oxygen levels. The Company is a participant in FDA’s “Coronavirus Treatment Acceleration Program,” intended to significantly shorten normal FDA review processes. Clinical trial start-up preparations continue as the Company awaits FDA’s formal response. On May 5, 2020, the Company announced the FDA notified the Company that it will accelerate the review of the Company’s pre-IND submission.

The Company is also currently working with other hospitals and regulatory authorities both in the U.S. and Eastern Europe to seek to forge the fastest possible pathway to TSC’s approval for the treatment of COVID-19 in those markets.

Acute Stroke

On Feb. 11, 2019, Diffusion announced the presentation of a poster detailing its innovative on-ambulance Phase 2 study with TSC for the treatment of acute stroke at the American Heart Association’s International Stroke Conference. The poster presented the design of the randomized, double-blind, placebo-controlled PHAST-TSC (Pre-Hospital Ambulance Stroke Trial-TSC) trial, which will enroll 160 suspected stroke patients at participating centers in Los Angeles and central Virginia. The primary trial endpoint is the extent of disability at 90 days. Safety endpoints include serious adverse events and all-cause mortality.

On Oct. 17, 2019, Diffusion announced that the first patient had been enrolled in this Phase 2 on-ambulance study. However, on March 24, 2020 Diffusion announced that it will experience delays in enrollment in the study due to the impact of the coronavirus on its research partners.
This disruption is expected to delay the Company’s previously announced two-year timeline for study completion.

**Glioblastoma Multiforme**

On July 23, 2019, Diffusion reported that based on favorable safety data in a 19 patient dose-escalation run-in study, the Data Safety Monitoring Board (DSMB) had recommended the continuation of the Company's Phase 3 clinical trial with trans sodium crocetinate (TSC) in inoperable glioblastoma multiforme (GBM) patients. In addition, the DSMB recommended that the highest dose administered, 1.5 mg/kg of TSC, be used during the adjuvant treatment period. On Dec. 10, 2019, the Company announced data signaling possible increased survival in inoperable glioblastoma multiforme (GBM) patients enrolled in the 19 patient in the lead-in study. The Company is seeking a partner to continue development of TSC in the inoperable GBM indication.

**Financing**

During 2019, Diffusion successfully completed three offerings (including, in certain instances, concurrent private placements), raising aggregate net proceeds of $11.8 million. Diffusion also raised approximately $3.9 million from the exercise of warrants to purchase its common stock during 2019. The proceeds from these offerings are targeted towards the continuation of the clinical development of TSC for serious, life-threatening, unmet medical needs and other corporate purposes.

**Intellectual Property**

On May 23, 2019, Diffusion announced receipt from the European Patent Office of a Notice of Intention to Grant a patent related to the use of the Company’s lead compound trans sodium crocetinate (“TSC”) in combination with the leading thrombolytic, tissue plasminogen activator (“tPA”), in the treatment of ischemic stroke. The patent claim covers administration of TSC within three or four hours of the onset of stroke symptoms in combination with tPA administered within nine to 12 hours of the onset of stroke symptoms.

The European Patent Office has also granted two additional patents to Diffusion. Patent, No. EP1667954B1 entitled “Bipolar Trans Carotenoid Salts and Their Uses” covers the use of bipolar trans-carotenoids, including TSC, to treat acute lung injury, congestive heart failure, and pretreatment or treatment during or after surgery. Patent No. EP 1487774B1, also entitled “Bipolar Trans Carotenoid Salts and Their Uses,” relates to methods of synthesizing bipolar trans carotenoid salts, including TSC. Similar patents were previously issued in the U.S.

**NASDAQ Compliance**

Recently, the Company’s stock moved below the $1.00 per share price required by NASDAQ to retain our listing status; however, de-listing can be avoided by means of a reverse stock split, which would have the effect of bringing the stock price above the required $1.00 per share mark to maintain its NASDAQ listing. As reflected in the accompanying Proxy Statement, the Company is seeking stockholder approval for the flexibility to conduct such a reverse stock split.
later in the year, if necessary. I urge you to approve the Board of Directors’ proposal to conduct a reverse stock split, potentially protecting the Company’s ability to retain its NASDAQ listing.

Retirement of Chief Medical Officer

On March 12, 2020, Diffusion announced the retirement of Professor John L. Gainer, Ph.D., the company’s chief science officer. Dr. Gainer will continue to serve as both an advisor to the Company and as a member of the board of directors. We thank Dr. Gainer for his many years of service to the Company and are thankful to have his continued experience on the board of directors.

Other

Diffusion is also continuing its development program for RES-529, the Company’s PI3K/AKT/mTOR pathway inhibitor that dissociates the mTORC1 and mTORC2 complexes, with a focus on the preclinical testing phase for GBM.

More information on all of these developments is available in the press release section of our Website at www.diffusionpharma.com.

Again, I want to extend my sincere thanks to all our investors for your continued support. The Diffusion team remains fully committed to advancing the clinical development of TSC for the improved treatment of life-threatening unmet medical needs.

I encourage you to read the enclosed Proxy Statement and related materials and vote in favor of the proposals contained therein.

Sincerely,

David G. Kalergis
Chairman and CEO