Zacks Small-Cap Research

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Diffusion Pharmaceuticals Inc. (DFFN-NASDAQ)

DFFN: Animal Toxicology Testing of TSC Successfully Completed in Preparation of Phase 3 Clinical Trial; Uplist to the Nasdaq Complete…

Based on our probability adjusted DCF model that takes into account potential future revenues from TSC in GBM, pancreatic cancer, and brain metastases, DFFN is valued at $22/share. This model is highly dependent upon the continued clinical success of TSC and will be adjusted accordingly based upon future clinical results.

Current Price (11/28/16)	$3.54
Valuation	**$22.00**

OUTLOOK

On November 14, 2016, Diffusion Pharmaceuticals, Inc. announced financial results for the third quarter of 2016 and provided a business update. The company exited the quarter with $3.0 million in cash and cash equivalents, which we estimate will be sufficient to fund operations into the first quarter of 2017.

The company recently completed all required dosing for animal toxicity studies in support of the upcoming Phase 3 clinical trial of TSC in newly diagnosed GBM patients. During the third quarter, Diffusion completed a 1-for-10 reverse stock split and successfully uplisted to the Nasdaq stock exchange. This was an important milestone for the company as it should enhance the company's visibility and aid in attracting new investors.

SUMMARY DATA

52-Week High	**$17.00**
52-Week Low	**$3.54**
One-Year Return (%)	**-28.49**
Beta	**-0.20**
Average Daily Volume (sh)	**575**
Shares Outstanding (mil)	**10**
Market Capitalization ($mil)	**$37**
Short Interest Ratio (days)	**N/A**
Institutional Ownership (%)	**0**
Insider Ownership (%)	**19**
Annual Cash Dividend	**$0.00**
Dividend Yield (%)	**0.00**
5-Yr. Historical Growth Rates	
Sales (%)	**N/A**
Earnings Per Share (%)	**N/A**
Dividend (%)	**N/A**
P/E using TTM EPS	**N/A**
P/E using 2016 Estimate	**N/A**
P/E using 2017 Estimate	**N/A**

Risk Level	**High,**
Type of Stock	**Small-Growth**
Industry	**Med-Biomed/Gene**

ZACKS ESTIMATES

Revenue

(In millions of $)

	Q1 (Mar)	Q2 (Jun)	Q3 (Sep)	Q4 (Dec)	Year (Dec)
2015	0 A	0 A	0 A	0 A	0 A
2016	0 A	0 A	0 A	0 E	0 E
2017					0 E
2018					0 E

Earnings per Share

(EPS is operating earnings before non-recurring items)

	Q1 (Mar)	Q2 (Jun)	Q3 (Sep)	Q4 (Dec)	Year (Dec)
2015	-$0.60 A	-$0.60 A	-$0.70 A	-$1.20 A	-$3.10 A
2016	-$0.62 A	-$0.37 A	-$0.53 A	-$0.34 E	-$1.69 E
2017					-$0.86 E
2018					-$1.16 E

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WHAT'S NEW

Business Update

Diffusion Pharmaceuticals Inc. is a biopharmaceutical company focused on the development of treatments that augment the effects seen from current standard of care cancer therapies. The company's lead compound is trans sodium crocetinate (TSC), a small molecule that improves the diffusion of oxygen through the bloodstream in order to increase tissue oxygenation. This increase in oxygenation results in increased efficacy for radiation and chemotherapeutic cancer treatments, particularly for those that target hypoxic tumors such as glioblastoma multiforme (GBM) and pancreatic cancer. The company is currently in the final planning stages for a Phase 3 clinical trial of TSC in newly diagnosed GBM patients.

Background on TSC

TSC is a small molecule compound that directly affects the diffusion of oxygen through the blood plasma in order to increase its availability to hypoxic tissues. It is believed that TSC alters the molecular arrangement of water molecules in the plasma (which is composed of 90% water), with the altered structure being less dense than untreated plasma. For water, an increase in structure results in a decrease in density (for example, ice is less dense than liquid water). Applying this to plasma, since it is composed of approximately 90% water, increasing the structure of water molecules in plasma would result in a decrease in plasma density and an increased ability for oxygen molecules to diffuse through it. Both computer simulations (Laidig *et al*., 1998) and physical experimentations (Stennett *et al*., 2007) have shown that TSC increases water structure and results in additional hydrogen bonds being formed per water molecule, which leads to an increase in the diffusivity.

Glioblastoma Multiforme

Glioblastoma multiforme (GBM) is the most aggressive of the category of tumors known as gliomas, which all arise from glia cells within the central nervous system. There are four grades of gliomas, with the highest grade, Grade 4 or GBM, being the most aggressive and the most common form in humans. Unfortunately, most patients with GBM don't live much longer than one or two years, and this has not changed appreciably over the years. The reason these tumors are so difficult to treat is multi-dimensional and has to do with both the genetic make-up of the tumor (most GBM cells have multiple activating mutations and other genetic anomalies) as well as the way the tumors grow (they are highly infiltrative and arise in many different regions of the brain).

Current standard-of-care (SOC) treatment for GBM consists of surgery to resect as much of the tumor as possible followed by radiation therapy (RT) and chemotherapy (temozolomide, TMZ) to kill any tumor cells that were not removed through surgery. While some types of solid tumors can be cured surgically, this is very rare in GBM due to the diffuse nature of the tumor.

TSC Phase 1/2 Clinical Trial in GBM

The Phase 1/2 clinical trial in GBM enrolled 59 patients with newly diagnosed disease that received TSC in conjunction with radiation and TMZ (Gainer *et al*., 2016). In the Phase I portion of the trial, TSC was initially administered three times per week at half-dose to three patients prior to radiation. Six additional patients received full dose TSC for six weeks in combination with radiation. No dose-limiting toxicities were identified in the nine patients during the Phase I portion of the trial. Fifty additional patients were enrolled in the Phase II trial at full dose TSC in combination with TMZ and RT. Four weeks after completion of RT, all patients resumed TMZ for five days every four weeks, but no further TSC was administered.

The results of the study were presented in relation to a historical control group, which is from a 2005 study that showed the addition of TMZ to standard of care (surgery plus radiation) increased overall survival from 12.1 months to 14.6 months (Stupp *et al*., 2005). Diffusion reported that:

- TSC plus radiation and TMZ increased the patients' chance of survival at two years by 37% compared to the historical control group. The overall survival at two years was 37% in the TSC group compared to 27% in the historical control group.

- ❖ In the subgroup of patients considered inoperable, the chance of survival at two years for those who received TSC was increased by over 100 percent, as 40 percent in the TSC group were alive at two years compared to less than 20 percent in the control.

- ❖ 71 percent of people treated with TSC were alive at one year compared to 61 percent of people in the historical control group.

- ❖ Of the 37 patients with tumors able to be monitored, 27 experienced tumor regression, with 11 (30%) patients having complete tumor regression.

- ❖ No serious negative safety findings attributed to TSC were observed in the TSC study and adverse events were consistent with those seen in previous trials of GBM featuring radiation and TMZ.

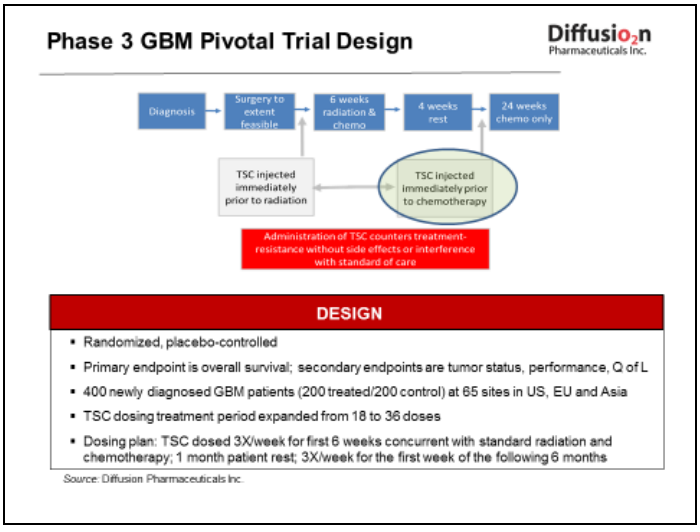
Since the study lacked a control arm it is difficult to draw definitive conclusions regarding the activity of TSC, however we have been unable to identify another publication that discusses tumor regression in GBM patients, thus it is difficult to put this data fully into context. Gainer *et al*. cite anecdotal evidence of a maximum regression of 25% typically seen with standard RT through discussions with those who administer RT to GBM patients, thus 30% of patients experiencing complete tumor regression appears to be unprecedented.

Planning for Phase 3 Clinical Trial in GBM

In preparation for a Phase 3 clinical program for TSC in GBM, Diffusion held an end of Phase 2 meeting with the FDA. At the meeting, FDA guidance was received on the trial design for the Phase 3 program, which included:

- ✓ A single, successful trial could serve as the basis for an application for approval
- ✓ The trial will be randomized, placebo controlled, multi-center clinical
- ✓ The trial will consist of 400 newly diagnosed GBM patients with half given TSC in conjunction with standard of care RT and TMZ
- ✓ There is significant leeway to increase TSC dosing exposure based on the Phase 1/2 safety results and supporting toxicology, which means that TSC can be used for both the radiation + chemotherapy and subsequent chemotherapy-only phase of GBM treatment

One of the major differences between the Phase 3 trial and the Phase 1/2 trial is the addition of TSC doses during chemotherapy. In the Phase 1/2 trial, TSC was only given prior to radiation (18 doses total), however in the Phase 3 study, the company is planning to give the patients 36 total doses of TSC, 18 in conjunction with radiation and 18 in conjunction with chemotherapy. The following figure gives a graphical representation of the Phase 3 trial.



Since the company is increasing the planned number of doses of TSC from 18 to 36, expanded toxicology studies were performed. On September 19, 2016, Diffusion announced the successful completion of those studies. A Chemistry, Manufacturing, and Controls (CMC) amendment will also be submitted to the FDA describing the cGMP production of TSC. With the toxicology studies complete and assuming availability of the required financial resources, we believe this will allow for the first patient to be dosed in the Phase 3 trial in mid-2017. The primary endpoint of the study is overall survival, and we expect topline results to be available in the first half of 2020.

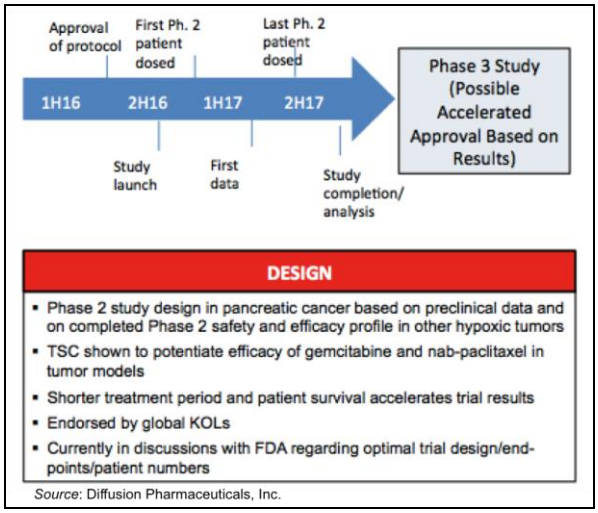
TSC for Pancreatic Cancer

Pancreatic cancer is responsible for 7% of all cancer deaths in both men and women, making it the fourth leading cause of cancer death in the U.S. (American Cancer Society). Due to differences in locations of the tumors and their proximity to nearby blood vessels, only 20% of cases are eligible for surgery. Of the tumors that are surgically resected, 80% of those patients will still develop metastatic disease within two to three years following surgery (Daniel *et al*., 2008). For those with pancreatic cancer that cannot be surgically removed, the median overall survival is 10 to 14 months. For those with Stage IV disease (meaning the cancer has metastasized), the 5-year survival rate is just 1%.

Gemcitabine is the SOC chemotherapy agent for metastatic pancreatic cancer. The FDA has approved its use in combination with two other chemotherapeutic agents: erlotinib (Tarceva®) and nab-paclitaxel (Abraxane®). FOLFIRINOX (leucovorin + 5-fluorouracil + oxaliplatin + irinotecan) is a combination regimen that significantly improved overall survival compared to treatment with gemcitabine (11.1 months vs. 6.8 months) (Conroy *et al*., 2011). However, treatment with FOLFIRINOX is accompanied by serious adverse events, and for that reason is only recommended for the healthiest patients. Onivyde® (irinotecan liposome injection) was approved by the FDA in 2015 in combination with fluorouracil and leucovorin to treat patients with metastatic pancreatic cancer who failed treatment with gemcitabine-based chemotherapy. In the pivotal clinical trial, patients treated with Onivyde® plus fluorouracil/leucovorin lived an average of 6.1 months, compared to 4.2 months for those treated with only fluorouracil/leucovorin.

In 2016, approximately 49,000 people will be diagnosed with pancreatic cancer in the U.S. More than half of these patients will be diagnosed with metastatic disease. As previously noted, the 5-year survival rates for patients with pancreatic cancer are dismal (<14%) and are particularly bad for those with metastatic disease (~1%), thus indicating the need for more effective treatment options for these patients.

The Phase 2 clinical trial for TSC in pancreatic cancer is based on the successful Phase 1/2 clinical trial in GBM as well as the fact that pancreatic tumors are usually highly hypoxic. Global experts in the field of pancreatic cancer agree that pancreatic cancer is the most appropriate target for expansion of the use of TSC, and a clinical advisory board of these key opinion leaders has been assembled to facilitate the pancreatic cancer clinical trial. The company is currently continuing discussions with the FDA regarding trial design/end-points/patient numbers. The figure below gives an overview of the proposed study.



TSC for Brain Metastases

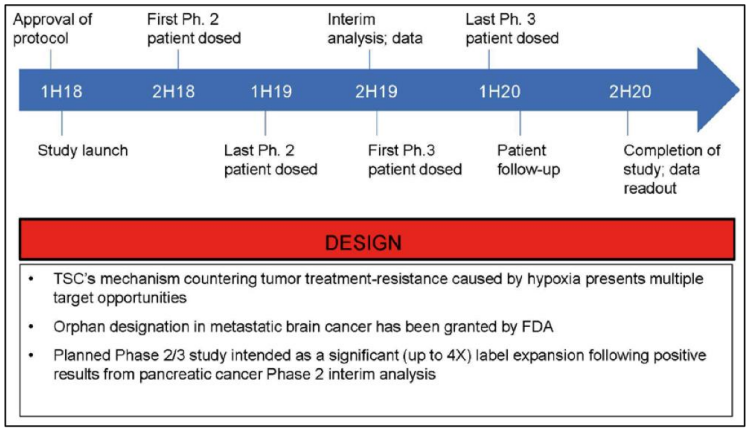
Metastatic brain cancer occurs when a primary tumor spreads to the brain. Primary brain cancers, such as GBM, are relatively rare, however metastatic brain tumors are much more common and represent a life-threatening complication for many different types of cancer. Up to 30% of adult cancer patients will suffer from brain metastases (Norden *et al*., 2005). While an exact figure is difficult to determine, it is estimated that 170,000 cases of metastatic brain cancer occur every year in the U.S. Lung cancer is the type of cancer most likely to metastasize to the brain, followed by kidney and skin cancer (Schouten *et al*., 2002). Just as with primary brain cancers, the prognosis for

patients with brain metastases is very grim. Median overall survival for those with brain metastases is less than one year (Sundström *et al*., 1998).

The most pressing issue for patients with brain metastases is getting symptoms under control, which are typically brought on by the presence of a tumor putting pressure on the surrounding region of the brain. Symptoms can include headaches, speech difficulties, seizures, and visual disturbances. Corticosteroids are often used to control swelling and anti-epileptic medications are given to prevent the recurrence of seizures. Surgery can be performed if the tumor is located in a portion of the brain that allows it. Whole brain radiation therapy is utilized for most patients, however it is most effective for those with primary tumors that are more sensitive to it, such as lung and breast cancer. Chemotherapy is used sparingly due to the inability for the vast majority of those drugs to cross the blood-brain barrier in sufficient quantities to be effective. There are currently no FDA-approved medications for the treatment of brain metastases.

Plans for TSC Phase 2/3 Clinical Trial in Metastatic Brain Cancer

Diffusion is planning to utilize a Phase 2/3 clinical trial in metastatic brain cancer as a means of expanding the label significantly (4X). We anticipate the first patient being dosed in the Phase 2/3 metastatic brain cancer trial in the second half of 2018, an interim analysis to take place in 2019, and the data to be available in the second half of 2020. A timeline of expected events is shown below.



Source: Diffusion Pharmaceuticals, Inc.

Scientific Advisory Board

On September 29, 2016, Diffusion announced the creation of a Scientific Advisory Board (SAB) of distinguished scientists and clinicians to serve as a resource for the company as it continues development of TSC in a number of different indications. Members of the SAB include:

Guy Chisolm III, PhD – Professor in the Department of Cellular and Vice Chair of the Lerner Research Institute at Cleveland Clinic prior to his recent retirement.

Gene Barnett, MD, MBA, FACS – Director, Rose Ella Burkhardt Brain Tumor and Neuro-Oncology Center of the Cleveland Clinic Neurological Institute. Authored more than 210 articles in leading medical journals.

Connie Hess, MD, MHS – Assistant Professor of Medicine at the University of Colorado.

William Hiatt, MD – Endowed Professor for Cardiovascular Research at University of Colorado School of Medicine, Division of Cardiology.

Karen Johnston, MD – Harrison Distinguished Professor and Chair of Neurology and Professor of Public Health Sciences at the University of Virginia.

Jeffrey Saver, MD – Director of the UCLA Stroke Unit and Professor and SA Vice-Chair of Neurology at the David Geffen School of Medicine.

Kathleen Welsh-Bohmer, PhD – Director of the Joseph and Kathleen Bryan Alzheimer's Disease Research Center at Duke University Medical Center.

Financial Update

On November 14, 2016, Diffusion announced financial results for the third quarter of 2016. As expected, the company did not report any revenues. The company reported R&D expenses of $1.9 million and G&A expenses of $3.9 million, compared with R&D expenses of $0.9 million and G&A expenses of $0.4 million for the same time period in 2015. The increase in R&D expenses was due to a $1.0 million noncash impairment charge upon abandoning the future development of RES-440 (a legacy compound acquired from the reverse merger with RestorGenex Corp). The increase in G&A expenses was primarily due to a $2.5 million noncash charge upon the settlement of a litigation proceeding and a $0.5 million increase in professional fees as a result of operating as a public company.

Net loss for the third quarter of 2016 was $5.4 million, or $0.53 per share. Actual cash burn during the quarter was $1.9 million. As of September 30, 2016, the company had approximately $3.0 million in cash and cash equivalents, which we estimate will be sufficient to fund operations into the first quarter of 2017.

In September 2016, the company sold convertible promissory notes in an aggregate principal amount of $1.88 million. The notes have a one year term and an interest rate of 6.0%. At any time prior to the maturity date, the holders may elect to convert the notes into shares of the company's common stock at a conversion price of $3.50 per share.

On August 18, 2016, Diffusion announced a 1-for-10 reverse stock split that reduced the number of outstanding shares of common stock from approximately 103.5 million to 10.3 million. On November 8, 2016, the company announced that shares of its common stock were approved for listing on the Nasdaq Capital Market. This was an important milestone for the company and will likely enhance the company's visibility and help to attract new investors

Valuation

Diffusion's valuation is derived from a risk-adjusted discounted cash flow model that takes into account potential future revenues from the sale of TSC in GBM, pancreatic cancer, and brain metastases. For all indications we assume that the company will partner and receive 15% royalties on net sales.

For GBM, we model for the Phase 3 trial to initiate in 2017, a new drug application (NDA) to be filed in 2021, and approval in 2022. If successful, we believe TSC would quickly be incorporated into standard of care for newly diagnosed patients. Using these assumptions the company would likely attain a sizeable share of the market (perhaps up to 75-80% peak market share), which would lead to worldwide sales of approximately $900 million. Applying a 15% discount rate and a 60% probability of approval leads to a net present value for TSC in GBM of $101 million.

For pancreatic cancer, we model for the Phase 2 trial to initiate in 2017, an NDA filing in 2021, and approval in 2022. Just as with GBM, if TSC proves to be successful when added to the standard of care for pancreatic cancer, we believe the company could attain peak market share of up to 50%. We model for this to translate into peak sales of approximately $1.5 billion worldwide. Applying a 15% discount rate and a 33% probability of success leads to a net present value for TSC in pancreatic cancer of $154 million.

For brain metastases, we model for a Phase 2/3 trial to initiate in 2019, an NDA filing in 2022 and approval in 2023. The brain metastases market is much larger than for primary brain cancer like GBM, thus even a 20% market share would lead to peak worldwide revenues of approximately $4 billion. Applying a 15% discount rate and a 33% probability of success leads to a net present value for TSC in brain metastases of $187 million.

Combing the net present value for each of the company's development programs along with current cash total and expected burn of $50 million leads to a net present value for the company of approximately $395 million. Following the reverse split, we estimate that the company will have a fully diluted share count of approximately Dividing that by the current fully diluted share count of 12.8 million shares, to which we add an additional five million shares to account for dilution, leads to a valuation of approximately $22 per share. The stock is currently trading at a significant discount to this valuation, and as more investors become aware of the potential for TSC, we believe the share price will increase to be more in alignment with our valuation.

PROJECTED FINANCIALS

Diffusion Pharmaceuticals, Inc.
Income Statement

Diffusion Pharmaceuticals, Inc.	2015 A	Q1 A	Q2 A	Q3 A	Q4 E	2016 E	2017 E	2018 E
TSC (GBM)	$0	$0	$0	$0	$0	$0	$0	$0
YOY Growth	-	-	-	-	-	-	-	-
TSC (Pancreatic Cancer)	$0	$0	$0	$0	$0	$0	$0	$0
YOY Growth	-	-	-	-	-	-	-	-
Grants & Collaborative Revenue	$0	$0	$0	$0	$0	$0	$0	$0
YOY Growth	-	-	-	-	-	-	-	-
Total Revenues	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**
YOY Growth	-	-	-	-	-	-	-	-
Cost of Sales	$0	$0	$0	$0	$0	$0	$0	$0
Product Gross Margin	-	-	-	-	-	-	-	-
Research & Development	$3.9	$2.4	$1.4	$1.9	$1.5	$7.2	$7.0	$10.0
General & Administrative	$2.5	$3.9	$2.3	$3.9	$2.0	$12.1	$4.0	$6.0
Other Expenses	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0
Operating Income	($6.4)	($6.2)	($3.8)	($5.8)	($3.5)	($19.3)	($11.0)	($16.0)
Operating Margin	-	-	-	-	-	-	-	-
Non-Operating Expenses (Net)	($0.3)	($0.0)	($0.0)	($0.0)	($0.0)	($0.0)	($0.2)	($0.2)
Pre-Tax Income	($6.7)	($6.2)	($3.8)	($5.8)	($3.5)	($19.4)	($11.2)	($16.2)
Income Taxes Paid	$0.0	$0	$0	($0)	$0	$0	$0	$0
Tax Rate	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*
Net Income	**($6.7)**	**($6.2)**	**($3.8)**	**($5.4)**	**($3.5)**	**($19.4)**	**($11.2)**	**($16.2)**
Net Margin	-	-	-	-	-	-	-	-
Reported EPS	**-**	**($0.62)**	**($0.37)**	**($0.53)**	**($0.34)**	**($1.89)**	**($0.86)**	**($1.16)**
YOY Growth	-	-	-	-	-	-	-	-
Basic Shares Outstanding	-	10.0	10.3	10.3	10.3	10.2	13.0	14.0

Source: Zacks Investment Research, Inc. *David Bautz, PhD*

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HISTORICAL STOCK PRICE



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