Zacks Small-Cap Research

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David Bautz, PhD
312-265-9471
dbautz@zacks.com

scr.zacks.com
10 S. Riverside Plaza, Chicago, IL 60606

Diffusion Pharmaceuticals Inc. (DFFN-NASDAQ)

DFFN: FDA Gives Final Guidance for Phase 3 Protocol for TSC in Inoperable GBM…

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 $7.50/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 (11/16/17)	$1.35
Valuation	**$7.50**

OUTLOOK

On October 17, 2017, Diffusion Pharmaceuticals, Inc. (DFFN) announced that the U.S. FDA had provided final protocol guidance for the company's Phase 3 clinical trial of trans sodium crocetinate (TSC) in patients with newly diagnosed inoperable glioblastoma multiforme (GBM). We anticipate the first patient enrolling in the trial before the end of 2017. A total of 236 patients will be randomized 1:1 to receive standard of care (radiation plus chemotherapy) with TSC or placebo. The trial will take place at a total of 100 clinical sites (54 in the U.S. and 46 in the E.U.). An interim analysis may be performed in 2020 with final results likely available in 2021.

SUMMARY DATA

52-Week High	**$8.35**
52-Week Low	**$1.31**
One-Year Return (%)	**-66.61**
Beta	**-0.75**
Average Daily Volume (sh)	**175,681**
Shares Outstanding (mil)	**15**
Market Capitalization ($mil)	**$20**
Short Interest Ratio (days)	**N/A**
Institutional Ownership (%)	**7**
Insider Ownership (%)	**16**
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)
2016	0 A	0 A	0 A	0 A	0 A
2017	0 A	0 A	0 A	0 E	0 E
2018					0 E
2019					0 E

Earnings per Share

(EPS is operating earnings before non-recurring items)

	Q1 (Mar)	Q2 (Jun)	Q3 (Sep)	Q4 (Dec)	Year (Dec)
2016	-$0.62 A	-$0.37 A	-$0.53 A	-$0.25 A	-$1.76 A
2017	-$2.77 A	$1.89 A	-$0.37 A	-$0.31 E	-$0.61 E
2018					-$1.07 E
2019					-$1.34 E

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WHAT'S NEW

Financial Update

On November 13, 2017, Diffusion Pharmaceuticals, Inc. (DFFN) announced financial results for the third quarter of 2017. As expected, the company did not report any revenues. Diffusion reported net income of $5.1 million, or $0.37 per share, which was the result of a non-cash gain of $8.4 million related to the change in the fair value of warrant liabilities due to a decrease in the fair market value of the company's common stock and not indicative of ongoing operations.

R&D expenses were $1.8 million in the third quarter of 2017 compared to $1.9 million for the third quarter of 2016. The decrease was due to decreased expenses attributable to animal toxicology studies and an impairment charge recognized in the third quarter of 2016 partially offset by an increase in drug manufacturing and GBM trial costs. G&A expenses were $1.6 million in the third quarter of 2017 compared to $3.9 million for the third quarter of 2016. The decrease was due primarily to a decrease in litigation settlement fees partially offset by an increase in salary and stock-based compensation.

Diffusion exited the third quarter of 2017 with approximately $11.2 million in cash and cash equivalents. We estimate the company currently has sufficient capital to fund operations into the second quarter of 2018. At least one additional financing will be necessary to fully fund the upcoming Phase 3 clinical trial of TSC in GBM.

As of November 10, 2017, Diffusion had approximately 14.5 million shares of common stock, 8.3 million shares of Series A Preferred stock that can be converted into 8.3 million shares of common stock, 0.8 million shares due upon conversion of debt, 2.5 million stock options, and 14.0 million warrants for a fully diluted share count of approximately 40.2 million.

Business Update

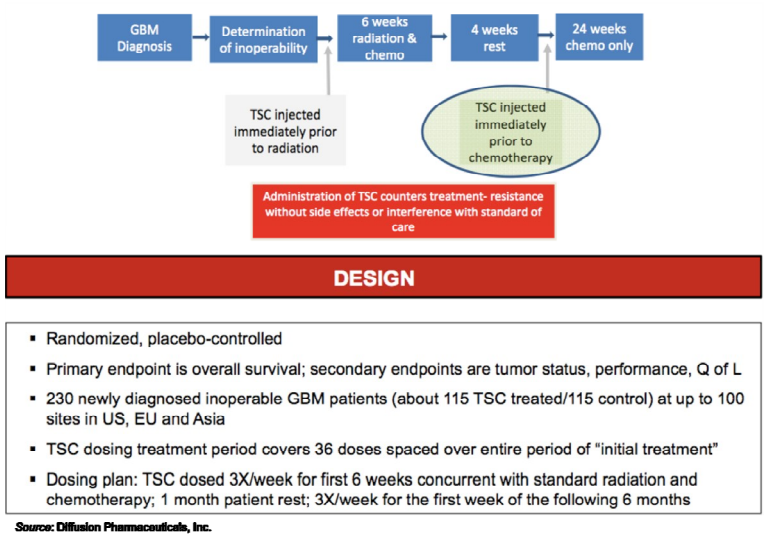
Diffusion Pharmaceuticals, Inc. is a biopharmaceutical company focused on the development of treatments that augment the effects seen from current standard of care cancer therapies. The company's lead compound is trans sodium crocetinate (TSC), a small molecule that improves the diffusion of oxygen through 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. We anticipate a Phase 3 clinical trial of TSC in newly diagnosed inoperable GBM patients to initiate before the end of 2017.

Phase 3 Clinical Trial of TSC in GBM Patients

On October 17, 2017, Diffusion announced that the FDA has provided final protocol guidance for the upcoming Phase 3 clinical trial of TSC in patients with newly diagnosed inoperable GBM. The company decided to focus on patients with inoperable GBM for the following reasons:

- ✓ The Phase 1/2 clinical trial showed a 380% increase in survival at two years in inoperable patients compared to a historical control group.
- ✓ The number of patients required will only be 236, compared to approximately 400 that would be required if all newly diagnosed GBM patients were included.
- ✓ Inoperable GBM patients fare much worse using SOC treatment and need better treatment options.
- ✓ Reducing the number of patients will provide significant cost savings.

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.



Source: Diffusion Pharmaceuticals, Inc.

We anticipate the first patient being enrolled before the end of 2017, with an interim analysis potentially taking place in 2020 and final results from the trial likely to be released in 2021.

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 of oxygen.

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 (biopsy only), the chance of survival at two years for those who received TSC was increased by 380%.

- 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.

New Chief Business Officer

On Aug. 23, 2017, Diffusion announced the hiring of William Hornung for the newly formed position of Chief Business Officer. Mr. Hornung has over 20 years of finance and leadership experience in the biopharmaceutical industry. He was previously at Contravir Pharmaceuticals where he served as Chief Financial Officer, during which time he helped the company uplist to the Nasdaq and raise nearly $30 million. Prior to Contravir, Mr. Hornung held various positions of increasing responsibility at PTC Therapeutics, most recently as Vice President of Finance. Mr. Hornung's vast experience with raising capital and leading operations at emerging biopharmaceutical companies will be an important addition as Diffusion becomes a 'Phase 3' company.

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. For pancreatic cancer, we model for the Phase 2 trial to initiate in 2018, an NDA filing in 2022, and approval in 2023. For brain metastases, we model for a Phase 2/3 trial to initiate in 2020, an NDA filing in 2023 and approval in 2024.

Combing the net present value for each of the company's development programs along with the company's current cash position and estimated additional capital necessary leads to a net present value for the company of approximately $300 million. Dividing that by the estimated fully diluted share count of 40.1 million shares leads to a valuation of approximately $7.50 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.	2016 A	Q1 A	Q2 A	Q3 A	Q4 E	2017 E	2018 E	2019 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	$7.3	$1.0	$1.2	$1.8	$2.0	$5.9	$10.0	$17.0
General & Administrative	$11.1	$1.6	$1.8	$1.6	$2.5	$7.4	$9.0	$9.5
Other Expenses	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0
Operating Income	($18.4)	($2.6)	($3.0)	($3.3)	($4.5)	($13.4)	($19.0)	($26.5)
Operating Margin	-	-	-	-	-	-	-	-
Non-Operating Expenses (Net)	($0.0)	($26.1)	$23.4	$8.4	($0.0)	$5.8	($0.2)	($0.2)
Pre-Tax Income	($18.4)	($28.6)	$20.4	$5.1	($4.5)	($7.6)	($19.2)	($26.7)
Income Taxes Paid	($0)	$0	$0	$0	$0	$0	$0	$0
Tax Rate	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*
Net Income	**($18.0)**	**($28.6)**	**$20.4**	**$5.1**	**($4.5)**	**($7.6)**	**($19.2)**	**($26.7)**
Net Margin	-	-	-	-	-	-	-	-
Reported EPS	**($1.76)**	**($2.77)**	**$1.89**	**$0.37**	**($0.31)**	**($0.61)**	**($1.07)**	**($1.34)**
YOY Growth	-	-	-	-	-	-	-	-
Basic Shares Outstanding	10.2	10.3	10.8	13.9	14.5	12.4	18.0	20.0

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

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