Zacks Small-Cap Research

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Diffusion Pharmaceuticals Inc. (DFFN-NASDAQ)

DFFN: Focusing on Inoperable GBM Patients for Phase 3 Trial of TSC…

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 $10/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 (05/25/17)	$2.80
Valuation	**$10.00**

OUTLOOK

On May 15, 2017, Diffusion Pharmaceuticals, Inc. (DFFN) announced financial results for the first quarter of 2017. The company reported a net loss of $28.6 million, or $2.77 per share, however that loss included $26.0 million in warrant related expense, including $25.6 million in non-cash expenses. The company exited the quarter with $12.2 million in cash and cash equivalents and received $8.3 million of net proceeds on Apr. 3, 2017 from a $25.0 million private placement that closed on Mar. 31, 2017.

We anticipate the company initiating a Phase 3 clinical trial for trans sodium crocetinate (TSC) in patients with inoperable glioblastoma multiforme (GBM) in the fourth quarter of 2017. By focusing on inoperable GBM patients, the patient number for the Phase 3 trial should be reduced from over 400 to approximately 230, providing significant cost savings.

SUMMARY DATA

52-Week High	**$15.50**
52-Week Low	**$0.80**
One-Year Return (%)	**-68.44**
Beta	**-1.00**
Average Daily Volume (sh)	**361,424**
Shares Outstanding (mil)	**10**
Market Capitalization ($mil)	**$29**
Short Interest Ratio (days)	**N/A**
Institutional Ownership (%)	**0**
Insider Ownership (%)	**22**
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 E	0 E	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	-$0.37 E	-$0.43 E	-$0.43 E	-$3.98 E
2018					-$1.37 E
2019					-$1.48 E

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WHAT'S NEW

Financial Update

On May 15, 2017, Diffusion Pharmaceuticals, Inc. (DFFN) announced financial results for the first quarter of 2017. As expected, the company did not report any revenues. Net loss for the first quarter of 2017 was $28.6 million, or $2.77 per share. R&D expenses were $1.0 million in the first quarter of 2017 compared to $2.4 million for the first quarter of 2016. The decrease was due to decreased expenses attributable to the pancreatic cancer program and animal toxicology. G&A expenses were $1.6 million in the first quarter of 2017 compare to $3.9 million for the first quarter of 2016. The decrease was due primarily to costs associated with the reverse merger transaction in 2016.

In connection with the private placement of Series A preferred stock and warrants, the company recognized $10.2 million in excess fair value of the common stock warrants over the gross proceeds from the private placement, $2.9 million in placement agent commission and other offering costs, and a $12.9 million expense for the change in fair value of the warrants due to an increase in the company's stock price. All together, the company had $25.6 million in non-cash charges during the first quarter of 2017.

Diffusion exited the first quarter of 2017 with approximately $12.2 million in cash and cash equivalents. On April 3, 2017, the company received $8.3 million of net proceeds from the private placement that closed on Mar. 31, 2017. We estimate the company currently has sufficient capital to fund operations into the second quarter of 2018. An additional financing will be necessary to fully fund the upcoming Phase 3 clinical trial of TSC in GBM.

As of May 5, 2017, Diffusion had approximately 10.3 million shares of common stock, 12.4 million shares of Series A Preferred stock that can be converted into 12.4 million shares of common stock, 0.7 million shares due upon conversion of debt, 2.3 million stock options, and 14.0 million warrants for a fully diluted share count of approximately 39.8 million.

Business Update

Diffusion 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 inoperable 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 (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.

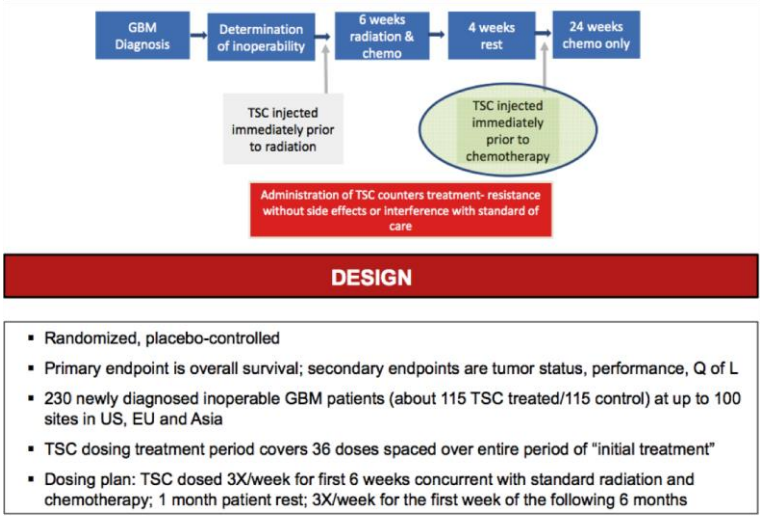
Since the study lacked a control arm it is difficult to draw definitive conclusions regarding the activity of TSC, however we have been unable to identify another publication that discusses tumor regression in GBM patients, thus it is difficult to put this data fully into context. Gainer *et al*. cite 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.

Planning for Phase 3 Clinical Trial in Inoperable GBM Patients

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, and the company now believes that focusing on inoperable patients is a prudent strategy 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 approximately 230, 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.

The company is currently waiting for the FDA to sign-off on the clinical trial protocol, and assuming that occurs in the third quarter of 2017, the trial should initiate before the end of 2017. An interim analysis could take place in 2019, with final results from the trial likely to be released in 2020.

Celator Acquisition Provides Example of Potential Outcome for Diffusion

Celator Pharmaceuticals, Inc. developed Vyxeos, a reformulation of the standard acute myeloid leukemia (AML) chemotherapy medications cytarabine and daunorubicin. Phase 2 results of Vyxeos in AML patients were only moderately positive, however the drug appeared to significantly help those in a subgroup with secondary AML. A confirmatory Phase 3 study in secondary AML patients showed increased overall survival from 5.95 months to 9.56 months, and 31.1% of patients receiving Vyxeos were alive at two years compared to just 12.3% of those receiving standard of care treatment. Following the release of the Phase 3 results, Celator was acquired by Jazz Pharmaceuticals (NASDAQ: JAZZ) for $30.25 per share, or $1.5 billion. Celator's stock had been trading as low as $1.12 per share ($48 million market cap) during the preceding year. Just as Celator did, Diffusion is focusing on a subset of patients that showed exceptionally strong results in an early stage clinical trial, and with positive Phase 3 results it is conceivable that Diffusion would attract a valuation much higher than it currently has.

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 2021, and approval in 2022. For brain metastases, we model for a Phase 2/3 trial to initiate in 2019, an NDA filing in 2022 and approval in 2023.

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 $400 million. Dividing that by the estimated fully diluted share count of 39.8 million shares leads to a valuation of approximately $10 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 E	Q3 E	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	$1.8	$2.0	$2.0	$6.8	$10.0	$17.0
General & Administrative	$11.1	$1.6	$2.0	$2.5	$2.5	$8.6	$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)	($3.8)	($4.5)	($4.5)	($15.4)	($19.0)	($26.5)
Operating Margin	-	-	-	-	-	-	-	-
Non-Operating Expenses (Net)	($0.0)	($26.1)	($0.0)	($0.0)	($0.0)	($26.1)	($0.2)	($0.2)
Pre-Tax Income	($18.4)	($28.6)	($3.8)	($4.5)	($4.5)	($41.5)	($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)**	**($3.8)**	**($4.5)**	**($4.5)**	**($41.5)**	**($19.2)**	**($26.7)**
Net Margin	-	-	-	-	-	-	-	-
Reported EPS	**($1.76)**	**($2.77)**	**($0.37)**	**($0.43)**	**($0.43)**	**($3.98)**	**($1.37)**	**($1.48)**
YOY Growth	-	-	-	-	-	-	-	-
Basic Shares Outstanding	10.2	10.3	10.4	10.4	10.5	10.4	14.0	18.0

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

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