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Diffusion Pharmaceuticals, Inc. (DFFN-NASDAQ)

DFFN: Evaluating TSC as Potential Treatment for ARDS…

Based on our probability adjusted DCF model that takes into account potential future revenues from TSC in stroke, DFFN is valued at $1.50/share. This model is highly dependent upon the continued clinical success of TSC and will be adjusted accordingly based upon future clinical results.

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Current Price (04/03/20)	$0.41
Valuation	**$1.50**

OUTLOOK

On April 1, 2020, Diffusion Pharmaceuticals, Inc. (DFFN) announced plans to evaluate the company's lead development asset, trans sodium crocetinate (TSC), in patients with acute respiratory distress syndrome (ARDS) associated with infection by the novel coronavirus, SARS-CoV-2. Multiple preclinical studies show that TSC increases oxygen availability, including in a model of acute lung injury, thus it may help to counteract the systemic hypoxemia caused by ARDS. Initial studies will take place at the University of Virginia, although discussions are underway with researchers at other institutions. The company has also begun discussions with the FDA about a regulatory path forward in ARDS and we anticipate the company providing additional updates as warranted.

SUMMARY DATA

52-Week High	**$5.90**
52-Week Low	**$0.22**
One-Year Return (%)	**-90.10**
Beta	**0.07**
Average Daily Volume (sh)	**7,933,522**
Shares Outstanding (mil)	**35**
Market Capitalization ($mil)	**$14**
Short Interest Ratio (days)	**N/A**
Institutional Ownership (%)	**10**
Insider Ownership (%)	**6**
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 2018 Estimate	**N/A**
P/E using 2019 Estimate	**N/A**

Risk Level	**Average**
Type of Stock	**Small-Value**
Industry	**Med-Biomed/Gene**

ZACKS ESTIMATES

Revenue
(In millions of $)

	Q1 (Mar)	Q2 (Jun)	Q3 (Sep)	Q4 (Dec)	Year (Dec)
2019	0 A	0 A	0 A	0 A	0 A
2020	0 E	0 E	0 E	0 E	0 E
2021					0 E
2022					0 E

Earnings per Share
(Diluted)

	Q1 (Mar)	Q2 (Jun)	Q3 (Sep)	Q4 (Dec)	Year (Dec)
2019	-$0.81 A	-$0.63 A	-$0.60 A	-$0.25 A	-$1.76 A
2020	-$0.08 E	-$0.08 E	-$0.09 E	-$0.10 E	-$0.35 E
2021					-$0.27 E
2022					-$0.26 E

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WHAT'S NEW

Business Update

Evaluating TSC as Treatment for ARDS

On April 1, 2020, Diffusion Pharmaceuticals, Inc. (DFFN) announced that the company will be evaluating its lead development compound, trans sodium crocetinate (TSC), for the treatment of acute respiratory distress syndrome (ARDS) as a result of infection with the novel coronavirus, SARS-CoV-2. ARDS results in the small blood vessels of the lung leaking fluid that fills up the alveoli, thus preventing proper oxygen exchange (Stevens *et al*., 2018).

There are many causes of ARDS, including infections (e.g., pneumonia), severe burns, pancreatitis, inhalation of smoke or chemicals, or other serious illnesses. An excessive inflammatory response appears to be involved in the pathogenesis of ARDS (Li *et al*., 2019). Current treatment options involve supportive care while the lungs heal, which involves oxygen therapy supplied through a ventilator. There are no pharmacological treatments specifically for ARDS and approximately 40% of hospitalized patients die from it (Siegel *et al*., 2020).

The current coronavirus epidemic is resulting in severe disease for a small percentage of patients, many of which end up on a ventilator as a result of ARDS. This can lead to a hypoxic environment in the patient signified by a low blood oxygen level and subsequent lack of oxygen in vital organs, thus a treatment that can increase oxygenation should help to alleviate these symptoms.

In a model of acute lung injury that mimics ARDS, TSC was shown to increase arterial PO_2 immediately after administration without affecting the lungs (Gainer *et al*., 2005). This is in addition to multiple other examples of TSC increasing oxygenation in animal models, including in hemorrhagic shock (Giassi *et al*., 2002) and in a 10% oxygen environment (Singer *et al*., 2000). Thus, we believe there is ample support for testing TSC in the treatment of ARDS.

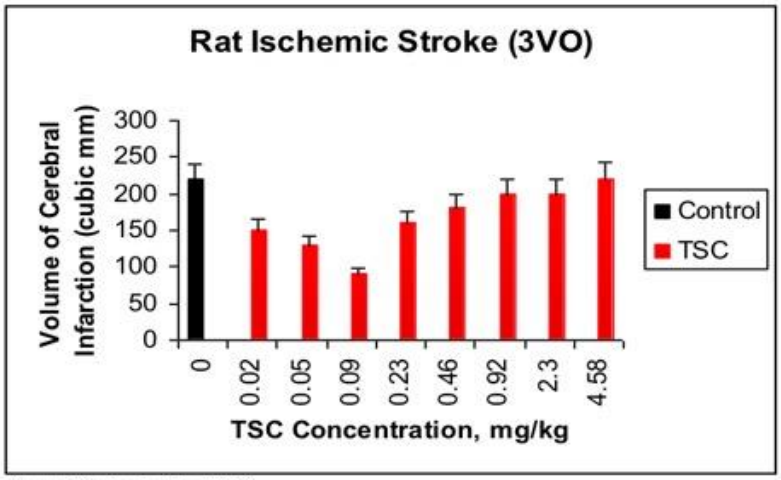
The company will initially be working with the University of Virginia (UVA) and the Integrated Translational Research Institute of Virginia (iTHRIV), however discussions are ongoing with researchers from other institutions who are interested in participating in the study. In addition, Diffusion has initiated discussions with the FDA on possible regulatory pathways for evaluating TSC in patients suffering from ARDS related to SARS-CoV-2 infection. We anticipate additional updates on this program in the coming months.

Update on Phase 2 Stroke Trial

Diffusion is currently conducting the the Phase 2 on-ambulance trial of the company's lead asset, trans sodium crocetinate (TSC), for the treatment of stroke. The Pre-Hospital Administration of Stroke Therapy-TSC (PHAST-TSC) trial is expected to enroll 160 patients who will be treated in the ambulance (80 active/80 placebo) within two hours of a suspected stroke on the way to the hospital regardless of whether they are suffering from an ischemic or hemorrhagic stroke. In addition, patients are eligible to receive tissue plasminogen activator (tPA) separately in-hospital if it is determined they are suffering from an ischemic stroke. A total of 23 hospitals, working in conjunction with 150 emergency medical transport groups, are expected to participate in the trial across central Virginia and in Los Angeles County. Enrollment has initiated in both locations, however on March 24, 2020, the company announced that they expect delays in enrollment due to the ongoing coronavirus pandemic. Specifically, the LA County Fire Department has ceased training of first responders that had been scheduled to participate in the trial due to the necessity to respond to the pandemic.

The primary endpoint of the study will be the extent of disability at 90 days using the utility-weighted modified Rankin Scale (UW-mRS) (Chaisinanunkul *et al*., 2015). Secondary endpoints will examine functional independence, activities of daily living, and health-related quality of life.

Preclinical models show that TSC could be an effective treatment for both ischemic and hemorrhagic stroke (Manabe *et al*., 2010; Wang *et al*., 2014). The following figure, shown at the 2019 International Stroke Conference, shows a dose dependent reduction in infarct volume in a rat model of ischemia-reperfusion where TSC was administered 10 minutes following onset of ischemia.



Source: Southerland *et al.*, 2019

In another rat model of ischemia-reperfusion, which involved two hours of ischemia followed by 22 hours of reperfusion, treatment with TSC one and a half hours after onset of ischemia led to a significant reduction in infarct volume of 32%. In a third model of ischemia-reperfusion, which involved two hours of reperfusion followed by an additional four hours of one vessel occlusion, treatment with TSC significantly reduced infarct volume by 34%. Lastly, in an intracerebral hemorrhage model in which TSC was administered three hours after collagenase injection, there was a significant reduction in hemispheric swelling and hemorrhage volume in animals treated with TSC. It is important that TSC be effective, or at least not detrimental, regardless of the type of stroke. Otherwise, its use would be contraindicated prior to the diagnosis of the type of stroke and by that time it may be too late to be effective.

There are approximately 800,000 strokes every year in the U.S., and they are responsible for the deaths of approximately 140,000 individuals (CDC). Strokes cost the U.S. healthcare system an estimated $34 billion every year (Benjamin *et al*., 2017).

Encouraging Data for Dose Escalation Run-in of Phase 3 GBM Trial

In December 2019, Diffusion announced the presentation of highly encouraging data from the 19 patient run-in portion of the Phase 3 **IN**vestigating **T**sc **A**gainst **C**ancerous **T**umors (INTACT) clinical trial of TSC in patients with glioblastoma (GBM). The data was presented by Diffusion's former Chief Scientific Officer, Dr. John Gainer, at the inaugural Glioblastoma Drug Development Summit, which took place from Dec. 10-11, 2019.

Patients in the INTACT trial have GBM but are not eligible for surgery, thus the standard of care treatment is radiation therapy for six weeks, followed by 28 days of rest, and then six cycles of temozolomide (TMZ). The INTACT protocol calls for patients to receive TSC both during radiation treatment and during the chemotherapy phase.

The company recently completed the 19-patient, open label, single arm, dose escalation run-in portion of the INTACT trial, which was required since a higher dose of TSC was to be administered, compared to the dose that was given during the Phase 1/2 trial in 59 newly diagnosed GBM patients (Gainer *et al*., 2016). The company reported that there were no safety signals associated with administration of TSC. The company reported that as of Mar. 10, 2020, five of the seven patients that received the highest dose of TSC during their treatment are still alive.

Patients with inoperable GBM have a very grim prognosis, thus the data presented by Diffusion is highly encouraging for this group of patients. In addition, there were no safety signals and TSC continues to be very well tolerated. The company is currently seeking a partner to continue development of TSC in GBM.

New European Patent for TSC

On February 7, 2020, Diffusion announced it was granted Patent Number EP2540696 B1 from the European Patent Office. The patent relates to pharmaceutical compositions of TSC and a cyclodextrin for use in therapy, with specific claims for the use of TSC in combination with radiation or chemotherapy. The patents broad claims and potential to cover additional indications for TSC could help to facilitate partner negotiations with a larger pharmaceutical company for the GBM indication.

Retirement of Dr. Gainer

On March 12, 2020, Diffusion announced that the company's Chief Scientific Officer, Dr. John Gainer, was retiring from his position and that a search would begin for a Chief Medical Officer as a replacement for the Chief Scientific Officer position. Dr. Gainer is the inventor of the trans bipolar carotenoid family of molecules, which includes TSC. He will remain as an advisor to the company and as a member of the Board of Directors.

Financial Update

On March 18, 2020, Diffusion announced financial results for the fourth quarter and full year 2019. As expected, the company did not report any revenues. R&D expenses were $6.6 million in 2019 compared to $5.8 million in 2018. The increase was primarily due to an increase in expenses related to the Phase 2 stroke trial and manufacturing expenses partially offset by a decrease in expenses related to the Phase 3 GBM trial. G&A expenses were $4.8 million in 2019 compared to $6.2 million in 2018. The decrease was primarily due to a decrease in stock-based compensation, salaries, and professional fees.

As of Dec. 31, 2019, Diffusion had approximately $14.2 million in cash and cash equivalents due to two financings in November and December of 2019. We estimate the company has sufficient cash to fund operations into the first quarter of 2021. As of March 12, 2020, Diffusion had approximately 34.6 million shares of common stock and when factoring in stock options and warrants a fully diluted share count of approximately 57.3 million.

Conclusion

We look forward to updates from the company regarding the use of TSC as a treatment for ARDS. The company has shown that TSC can increase oxygen levels in blood and tissue through a number of different preclinical models, thus we will be interested to see whether TSC proves effective in treating ARDS in patients suffering from COVID-19.

It's disappointing that the PHAST-TSC trial is going to experience delays in enrollment due to the coronavirus pandemic, however this is a problem for a large number of biotech companies and hopefully the impact will be minimal. Based on the large number of strokes that occur in the U.S. every year, and the billions of dollars that treating stroke victims costs the healthcare system each year, we believe that TSC could become a blockbuster drug in the treatment of stroke and we estimate for potential peak revenues of over $1 billion worldwide. However, we have reduced the value of the GBM indication in our valuation model as the company will not move forward in GBM without a partner, although with the encouraging data from the 19-patient run-in portion of the Phase 3 trial we believe the chances for a partnership have increased. Our valuation currently stands at $1.50 per share.

PROJECTED FINANCIALS

Diffusion Pharmaceuticals, Inc.	2019 A	Q1 E	Q2 E	Q3 E	Q4 E	2020 E	2021 E	2022 E
TSC (GBM)	$0	$0	$0	$0	$0	$0	$0	$0
YOY Growth	-	-	-	-	-	-	-	-
TSC (Stroke)	$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	$6.6	$1.5	$1.5	$1.7	$2.0	$6.8	$8.0	$10.0
General & Administrative	$4.8	$1.1	$1.2	$1.3	$1.3	$4.9	$5.2	$5.5
Goodwill Impairment	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0
Depreciation	$0.1	$0.0	$0.0	$0.0	$0.0	$0.1	$0.1	$0.1
Operating Income	($11.6)	($2.6)	($2.8)	($3.1)	($3.3)	($11.7)	($13.3)	($15.6)
Operating Margin	-	-	-	-	-	-	-	-
Non-Operating Expenses (Net)	$0.1	$0.0	$0.0	$0.0	$0.0	$0.0	($0.2)	($0.2)
Pre-Tax Income	($11.5)	($2.6)	($2.8)	($3.1)	($3.3)	($11.7)	($13.5)	($15.8)
Income Taxes	$0.3	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0
Accretion of Series A preferred dividends	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0
Tax Rate	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*
Net Income	**($11.8)**	**($2.6)**	**($2.8)**	**($3.1)**	**($3.3)**	**($11.7)**	**($13.5)**	**($15.8)**
Net Margin	-	-	-	-	-	-	-	-
Reported EPS	**($1.76)**	**($0.08)**	**($0.08)**	**($0.09)**	**($0.10)**	**($0.35)**	**($0.27)**	**($0.26)**
YOY Growth	-	-	-	-	-	-	-	-
Basic Shares Outstanding	6.7	34.0	34.0	34.0	34.0	34.0	50.0	60.0

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

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HISTORICAL STOCK PRICE



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