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

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

Oragenics, Inc.

(OGEN-AMEX)

OGEN: Phase 2 Trial of AG013 Adds Clinical Sites in Europe…

Based on our probability adjusted DCF model that takes into account potential future revenues from AG013 and OG716, OGEN is valued at $5.00/share. This model is highly dependent upon the continued clinical success of those programs and will be adjusted accordingly based upon future clinical outcomes.

Current Price (11/19/18)	$0.93
Valuation	**$5.00**

OUTLOOK

Oragenics, Inc. (OGEN) is currently conducting a Phase 2 clinical trial of AG013, an oral rinse solution containing genetically modified bacteria that secrete human Trefoil Factor 1 (hTFF1) that is designed to help protect and regenerate damaged epithelial cells of the mouth. The company recently announced a positive review by the Data Safety Monitoring Board (DSMB) and the addition of clinical trial sites in Germany, England, and Belgium. We continue to estimate that the trial will be completed in 2019.

Oragenics exited the third quarter of 2018 with approximately $13.8 million in cash and cash equivalents. Subsequent to the end of the quarter the company received approximately $9.5 million in proceeds from the exercise of 9.5 million warrants and as of Nov. 13, 2018 has approximately $22.3 million in cash.

SUMMARY DATA

52-Week High	**$4.41**
52-Week Low	**$0.38**
One-Year Return (%)	**-74.22**
Beta	**0.97**
Average Daily Volume (sh)	**2,369,000**
Shares Outstanding (mil)	**29**
Market Capitalization ($mil)	**$27**
Short Interest Ratio (days)	**N/A**
Institutional Ownership (%)	**17**
Insider Ownership (%)	**35**
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	**-0.3**
P/E using 2019 Estimate	**-0.5**

Risk Level	**High**
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)
2017	0 A	0 A	0 A	0 A	0 A
2018	0 A	0 A	0 A	0 E	0 E
2019					0 E
2020					0 E

Earnings Per Share

	Q1 (Mar)	Q2 (Jun)	Q3 (Sep)	Q4 (Dec)	Year (Dec)
2017	-$0.40 A	-$0.25 A	-$0.42 A	-$0.30 A	-$1.37 A
2018	-$0.42 A	-$0.38 A	-$0.35 A	-$0.10 E	-$0.81 E
2019					-$0.25 E
2020					-$0.21 E

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WHAT'S NEW

Business Update

Additional Clinical Trial Sites Open in Europe for Phase 2 Trial of AG013

Oragenics, Inc. (OGEN) is currently conducting a Phase 2, double blind, placebo controlled clinical trial of AG013 (NCT03234465). AG013 is an oral mouth rinse composed of a recombinant *Lactococcus lactis* strain that contains the coding sequence for human trefoil family factor 1 (hTFF1), which is continually secreted by the bacteria. The trefoil factor family (TFF) is a family of three different peptides secreted by epithelial cells of the gastrointestinal tract in response to injury (Hoffman, 2004). Their presence has been implicated in reducing chemotherapy- and radiation-induced injury, both in preclinical studies (Beck *et al*., 2004) and in clinical trials (Peterson *et al*., 2009).

Approximately 160-180 subjects with head and neck cancer receiving chemotherapy will receive either AG013 (2.0 x 10^{11} CFU) or placebo administered three times a day over 7-9 weeks (depending on the subject's chemotherapy plan). This will be followed by a four-week follow-up phase with a long-term follow up until 12 months past the end of chemotherapy treatment. OM will be assessed at the start of chemotherapy treatment and will continue until the subject has completed the short-term follow up phase or until OM resolves (WHO score ≤ 1). The purpose of the long-term follow up is to assess whether AG013 has any effect on the tumor response to chemotherapy treatment.

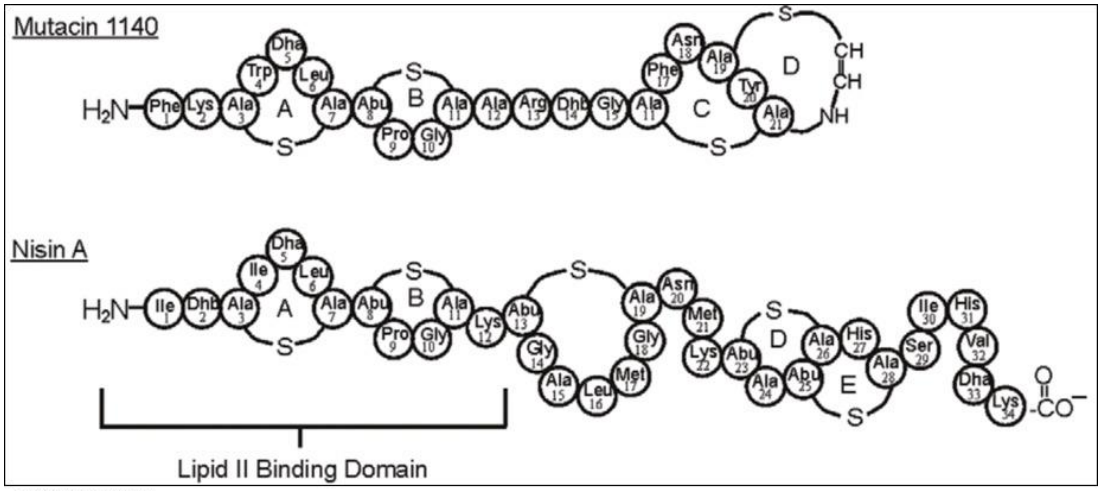
In August 2018, Oragenics announced that the Phase 2 trial was resuming following positive results from an interim safety analysis conducted by a Data and Safety Monitoring Board (DSMB) from 19 patients enrolled in the study. Safety was evaluated based on treatment-emergent adverse events, vital signs, weight, physical examinations, clinical assessments, and the presence/absence of AG013 in the blood. The Data Safety Monitoring Board (DSMB) concluded that the trial can continue with no changes to the study protocol. The incidence of adverse events between AG013 and placebo-treated patients was the same. Reports of serious adverse events were typical for a population of head and neck cancer patients undergoing chemotherapy and there were no reports of sepsis or bacteremia. Of particular note is the fact that only a few patients discontinued due to the development of severe OM, which could be an early indication of efficacy.

In October 2018, the company announced that it received clearance from the Belgian Health Authority to enroll Belgium residents in the Phase 2 trial and in November 2018 the company announced that it received clearance to enroll patients in both Germany and the United Kingdom. The addition of these clinical trial sites should facilitate enrollment of sufficient patients in the Phase 2 trial of AG013 such that the trial is completed in 2019.

Lantibiotics Program Presented at Boulder Peptide Symposium

In September 2018, Oragenics announced the presentation of data on its lantibiotics program at the Boulder Peptide Symposium. Lantibiotics are a class of peptide antibiotics that are produced by certain Gram-positive bacterial strains. The compounds range in size from 22 to 34 amino acids and typically go through a number of posttranslational modifications that results in novel serine and threonine derivatives, multiple types of sulfhydryl bonds, and the presence of the uncommon amino acids lanthionine (Lan) and B-methyllanthionine (MeLan), from which the lantibiotic name is derived. The compounds are classified based on their length, structure, and heat stability as Type A, Type B, Type IIa, and Type IIb.

Type A lantibiotics fall into two subcategories: compounds that are similar to nisin A (Gross *et al*., 1971) and those that are similar to mutacin 1140 (Smith *et al*., 2000). Nisin A is produced by *Lactobacillus lactis* while mutacin 1140 is produced by *Streptococcus mutans*. The structures of each of those compounds is shown below.



Source: Smith *et al.*, 2008

Lantibiotics exert their bactericidal activity through a number of different mechanisms, including transmembrane pore formation, lipid II-mediated pore formation, and lipid II abduction from physiological domains. Type A lantibiotics have a net positive charge, and it is believed that an electrostatic interaction between the positively charged lantibiotic and the negatively charged bacterial cell membrane is required for initial binding. In addition, Type A lantibiotics bind to lipid II (a precursor molecule in the synthesis of the bacterial cell wall) and cluster it away from the bacterial membrane where cell wall synthesis is occurring, thus ensuring that not enough lipid II is available and consequently inhibiting bacterial cell growth (Hasper *et al*., 2006). Mutacin 1140 does not appear to form pores like nisin A, thus suggesting that only sequestration of lipid II is responsible for its bactericidal activity. Vancomycin also targets lipid II, however it is at a unique site away from where lantibiotics bind. In addition, vancomycin does not sequester lipid II from its normal physiological locations (Daniel *et al*., 2003).

Scientists have been aware of lantibiotics for decades, however they have not been studied as extensively as other classes of antibiotics due to the difficultly in producing sufficient quantities of the compounds. As naturally occurring molecules, lantibiotics are usually produced and secreted into a cell's immediate environment, thus preventing other bacterial cells from infiltrating the area around them. When produced in culture there is a powerful feedback mechanism that works to prevent a bacterium from producing excess lantibiotic that would ultimately kill the host. This results in very low yields of lantibiotics when grown in culture, thus presenting a significant obstacle to their widespread commercial use. Oragenics overcame this obstacle by developing a methodology to produce sufficient quantities of lantibiotics, and through a collaboration with Intrexon Corp. it is developing a means to produce commercial-scale quantities of the drugs.

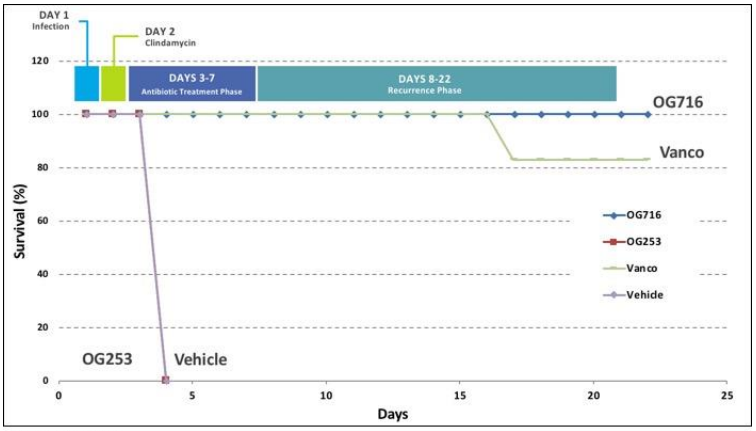
Development of OG716

Lantibiotic effectiveness was noted to be as good as penicillin against such strains as *Mycobacterium tuberculosis*, *Streptococcus pyogenes*, and *Staphylococcus aureus* back in the 1950's (Bavin *et al*., 1952). However, even then the authors of that study were aware of the difficulty in producing sufficient quantities of lantibiotics, and with no widespread antibiotic resistance there was not a pressing need for new classes of antibiotics.

Mutacin 1140 was first isolated from a *S. mutans* strain in the 1980's (Hillman *et al*., 1984). The molecule has a number of positive attributes from a therapeutic standpoint, as it is small, stable, and has a wide range of activity against most Gram-positive species. In addition, mutacin 1140 is rapidly bactericidal and thus far there have been no reports of spontaneous or chemically induced resistance.

While mutacin 1140 has good activity against a number of bacterial strains, Oragenics conducted a series of experiments to both gather data on the structure/function of the molecule and to determine if it could be therapeutically optimized (DeFusco *et al*., 2016). In order to do this, a 'saturation mutagenesis' experiment was performed, whereby all 22 amino acids of mutacin 1140 were each replaced with all the other 19 naturally occurring amino acids at each position. The top 41 variants were selected that had antimicrobial activity as good or better than mutacin 1140, of which seven were selected for testing in an *in vivo C. difficile* model. The variant OG253 was selected based on its ability to eradicate *C. difficile* infection. Unfortunately, OG253 is not orally active as the drug is degraded by digestive proteases. Thus, Oragenics selected a second compound, OG716, which is orally active. As shown in the following figure, treatment of hamsters infected with *C. difficile* with OG716 results in 100% survival.

This is in contrast to the vancomycin treated group, with only 82% survival, while all animals in the placebo and OG253 treated groups died within four days.



Source: Oragenics, Inc.

OG716 Development Plan

In 2017, Oragenics manufactured sufficient quantities of OG716 to be used in pre-IND studies and the first part of clinical development. The company is currently conducting pre-IND studies; single dose-escalating rat studies have completed and rat and monkey 14-day toxicology studies are under development. We anticipate the company filing an IND with the FDA in the second quarter of 2019, if sufficient capital is available to complete requisite studies, such that clinical trials can initiate in the second half of 2019 with the first indication being treatment of *C. difficile* infection.

Clostridium Difficile



Clostridium difficile

Clostridium difficile is a Gram-positive spore-forming bacterium that is best known for causing antibiotic-associated diarrhea. Some individuals harbor *C. difficile* as a normal part of their gut flora, however overgrowth of *C. difficile* and subsequent infection can occur when competing bacteria in the gut have been destroyed, as typically happens after a standard course of antibiotics. These infections typically occur in hospitalized or recently hospitalized patients who have been exposed to antibiotics. In addition, *C. difficile* can produce spores during times of stress, and these spores are capable of surviving extreme conditions such as high heat and household cleaners.

The CDC has designated *C. difficile* as an organism with a threat level of Urgent, with bacteria in this category representing an immediate public health threat that requires urgent and aggressive action. There are approximately 500,000 infections caused by *C. difficile* each year that result in 29,000 deaths. The number of deaths related to *C. difficile* infections increased 400% between 2000 and 2007, with more than 90% of deaths occurring in people aged 65 and older. In addition, *C. difficile* infections lead to $1 billion in excess health care costs each year. While antibiotic resistance is not yet a pressing concern with *C. difficile*, in 2000 a strain emerged that was resistant to fluoroquinolone antibiotics, which are commonly used to treat other infections.

Symptoms of *C. difficile* infection (CDI) are significant diarrhea, abdominal pain, fever and a distinctively foul stool odor. Pseudomembranous colitis (PMC) is the most severe form of the illness that results from a severe inflammatory response to *C. difficile* toxins. The pathogenicity of *C. difficile* is caused by multiple toxins, the best characterized of which are enterotoxin (*Clostridium difficile* Toxin-A) and cytotoxin (*Clostridium difficile* Toxin-B). The toxins are co-produced, with Toxin-A disrupting the cell cytoskeleton and Toxin-B activating signal transduction pathways of the immune system resulting in the diarrhea and inflammation associated with the illness. Treatment of CDI typically involves a course of antibiotics selected from one of the following:

- Metronidazole (Flagyl®): First-line treatment for mild to moderate CDI.
- Vancomycin (Vancocin®): Second-line treatment or first-line treatment for severe CDI.
- Fidaxomicin (DIFICID®): A narrow spectrum macrocyclic antibiotic that is non-systemic (minimally absorbed into the bloodstream), bactericidal, and results in little disruption to the normal intestinal flora.
- Rifaximin (Xifaxan®): This nonabsorbable antibiotic decreases the recurrence of diarrhea and *C. difficile* infection following treatment with metronidazole or vancomycin.

In addition to the above listed antibiotics, bezlotoxumab (Zinplava®), a monoclonal antibody targeting Toxin-B, is used to reduce the rate of recurrence of *C. difficile* infection in patients at high risk for recurrence.

Financial Update

On November 14, 2018, Oragenics announced financial results for the third quarter of 2018. As expected, the company did not record any revenues. The company reported a net loss in the second quarter of 2018 of $4.2 million, or $0.35 per share. R&D expenses for the third quarter of 2018 totaled $1.6 million compared to $1.0 million for the third quarter of 2017. The increase was primarily due to increased costs associated with the exclusive channel collaborations (ECC's) with Intrexon, including clinical trial costs for AG013. G&A expenses totaled $1.2 million for the third quarter of 2018 compared to $0.9 million for the third quarter of 2017. The increase was primarily due to increased stock-based compensation.

As of September 30, 2018, the company had approximately $13.8 million in cash and cash equivalents. In July 2018, Oragenics announced the closing of an underwritten public offering that resulted in net proceeds to the company of $12.3 million. This included the full exercise of the underwriter's over-allotment option to buy additional shares and warrants. In October 2018, the company received an additional $9.5 million in proceeds from the exercise of 9.5 million warrants, thus as of Nov. 13, 2018 the company had approximately $22.3 million in cash and cash equivalents.

As of Nov. 3, 2018, Oragenics had approximately 29.4 million shares of stock outstanding and when factoring in the Preferred shares, warrants, and stock options a fully diluted share count of approximately 39.3 million.

Valuation

We value Oragenics using a probability adjusted discounted cash flow model that takes into account future revenues from AG013 and OG716. For modeling purposes, we anticipate AG013 entering a Phase 3 trial in 2020, an NDA filing in 2022, and approval in 2023 in the U.S. and Europe, with approval one year later in Japan. For OG716, we forecast for clinical trials to start in 2019, an NDA filing in 2023, and approval in 2024.

There are approximately 700,000 newly diagnosed cancer patients in the U.S. that could potentially develop OM, with another 1.3 million in the E.U. and 20,000 in Japan. Patients who develop OM currently have few treatment options available to them outside of palliative care. We believe that a successful treatment that both prevented the incidence of OM and also decreased the incidence of severe OM in those that develop it would be very appealing to oncologists. An effective OM therapy could also decrease rates of hospitalizations for patients suffering severe OM and limit the need to decrease or stop therapy. We use a very conservative 5% peak market share, an average length of use of 60 days, and a cost of $100/day in the U.S. ($70/day and $75/day for the E.U. and Japan, respectively) to arrive at peak worldwide sales of approximately $350 million. Using a 13% discount rate and a 40% chance of approval leads to a net present value of $183 million.

For OG716, we estimate peak market share of 10% of the approximately 500,000, 200,000, and 100,000 *C. difficile* infections each year in the U.S., E.U., and Japan, respectively. We estimate the cost of treatment of $3,000, $2,000, and $2,250 for the U.S., E.U., and Japan, respectively. This leads to peak worldwide revenues of approximately $275 million. Using a 13% discount rate and a 25% chance of approval leads to a net present value of $14 million.

Combining the net present values for AG013 and OG716 along with the company's current cash position, potential cash from warrant exercises, and estimated cash burn leads to a net present value for the company of $185 million. Dividing by the fully diluted share count of 39.3 million leads to a current value of $5.00 per share.

PROJECTED FINANCIALS

Oragenics, Inc.	2017 A	Q1 A	Q2 A	Q3 A	Q4 E	2018 E	2019 E	2020 E
AGO13 (Oral Mucositis)	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**
OG716	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**
Licensing & Royalties	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**
Total Revenues	**$0.0**	**$0.0**	**$0.0**	**$0.0**	**$0.0**	**$0.0**	**$0.0**	**$0.0**
Cost of Sales	$0	$0	$0	$0	$0	$0	$0	$0
Product Gross Margin	-	-	-	-	-	-	-	-
Research & Development	$3.5	$1.3	$1.3	$1.6	$1.6	$5.8	$6.0	$6.4
General & Administrative	$3.2	$0.8	$1.0	$1.2	$1.0	$4.0	$4.0	$4.0
Other Operating Expenses	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0
Operating Income	($6.7)	($2.1)	($2.3)	($2.8)	($2.6)	($9.8)	($10.0)	($10.4)
Operating Margin	-	-	-	-	-	-	-	-
Non-Operating Expenses (Net)	($0.0)	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0
Pre-Tax Income	($6.7)	($2.1)	($2.3)	($2.8)	($2.6)	($9.7)	($10.0)	($10.4)
Income Taxes	$0	$0	$0	$0	$0	$0	$0	$0
Deemed Dividend of Series D Preferred	$0	$0	$0	$1	$0	$0	$0	$0
Net Income	($6.7)	($2.1)	($2.3)	($4.2)	($2.6)	($9.7)	($10.0)	($10.4)
Net Margin	-	-	-	-	-	-	-	-
Reported EPS	**($1.37)**	**($0.42)**	**($0.38)**	**($0.35)**	**($0.10)**	**($0.81)**	**($0.25)**	**($0.21)**
YOY Growth	-	-	-	-	-	*-40%*	*-69%*	*-17%*
Basic Shares Outstanding	4.9	5.0	6.0	11.9	25.0	12.0	40.0	50.0

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

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