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Oragenics, Inc

(OGEN-NYSE American)

OGEN: Initiating Coverage of Oragenics, Inc.; Developing a Novel Class of Antibiotics and Treatment for Oral Mucositis…

Based on our probability adjusted DCF model that takes into account potential future revenues from AG013 and OG716, OGEN is valued at $7.00/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 (06/11/18)	$1.55
Valuation	**$7.00**

OUTLOOK

Oragenics, Inc. (OGEN) is a biopharmaceutical company developing a new treatment for oral mucositis and novel antibiotic therapies for infectious diseases. The company's lead development product, AG013, is 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. AG013 is currently being studied in a Phase 2 clinical trial with results expected in mid-2019.

The company is also developing a novel class of antibiotic compounds known as lantibiotics. The lead lantibiotic compound, OG716, is being developed for the treatment of *Clostridium difficile* infection, which is responsible for 500,000 infections and 29,000 deaths per year. We anticipate an IND being filed for OG716 in 2Q19.

SUMMARY DATA

52-Week High	**$5.40**
52-Week Low	**$1.16**
One-Year Return (%)	**-64.77**
Beta	**1.27**
Average Daily Volume (sh)	**1,374,498**
Shares Outstanding (mil)	**6**
Market Capitalization ($mil)	**$9**
Short Interest Ratio (days)	**N/A**
Institutional Ownership (%)	**29**
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	**-0.6**
P/E using 2019 Estimate	**-0.7**

Risk Level	**High**
Type of Stock	**N/A**
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 E	0 E	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	-$0.45 E	-$0.41 E	-$0.47 E	-$1.64 E
2019					-$1.00 E
2020					-$0.80 E

WHAT'S NEW

Initiating Coverage

We are initiating coverage of Oragenics, Inc. (OGEN) with a $7.00 valuation. Oragenics is a biopharmaceutical company developing a new treatment for oral mucositis (OM) and a novel class of antibiotics.

Lead Drug is a Novel Solution to a Common Cancer Treatment Side Effect
AG013 is the company's lead product for the treatment of OM, a painful inflammation and ulceration of the lining of the mouth, throat, and esophagus that is one of the most common side effects of cancer chemotherapy and radiation treatment. AG013 is an oral rinse designed to deliver human Trefoil Factor 1 (hTFF1), which is secreted from a genetically modified Lactococcus species. We believe AG013 has a number of advantages over current OM treatments, including:

- **Ease of Administration**: AG013 is administered three times a day following a meal as an oral rinse.
- **Potential to Prevent OM**: There are no FDA approved therapies for the prevention of OM in a broad cancer population as current therapies are palliative in nature. In a Phase 1 study, AG013 treatment resulted in 29% of patients experiencing either 0 or 1 day of ulcerative OM compared to 0% of placebo-treated patients.
- **Low Cost of Goods**: Producing AG013 is very cost efficient as there are no peptides or proteins to purify.

Near-term Milestones including Interim Safety Data for Phase 2 Study of AG013
Oragenics is currently conducting a Phase 2 trial of AG013 in patients with head and neck cancer being treated with chemoradiation therapy. The company recently reported positive results from an interim safety analysis, and we anticipate completion of enrollment near the end of 2018 or early 2019 and topline data being reported in mid-2019.

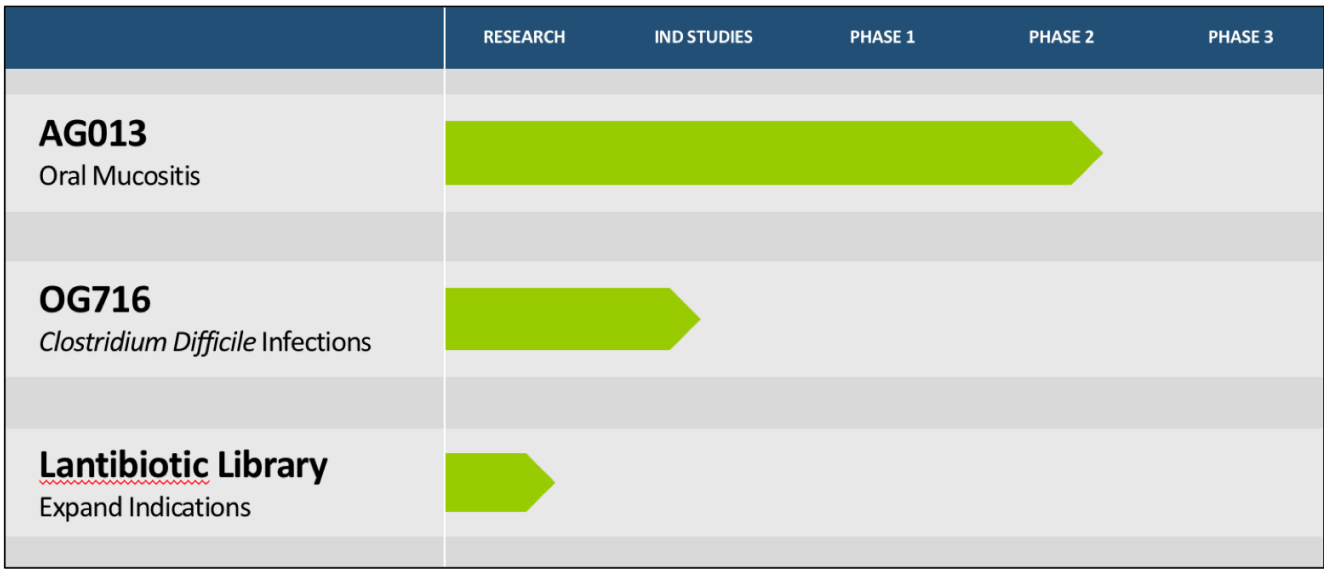
Developing a Novel Class of Antimicrobial Compounds
The widespread misuse and overuse of antibiotics has led to the development of a number of antibiotic resistant microbes, some of which that are resistant to multiple classes of drugs. Due to this, there is a desperate need for new antimicrobial compounds. Lantibiotics are a novel class of antimicrobial compounds that are active against multiple species of Gram-positive bacteria. Oragenics lead lantibiotic, OG716, is being developed for the treatment of *Clostridium difficile* infection. OG716, and the lantibiotic class of compounds, have a number of positive attributes, including:

- **Novel Mechanism of Action**: OG716 exerts its bactericidal activity through a unique mechanism of Lipid II binding and sequestration, which renders the microbe unable to synthesize the cell wall and leads to rapid cell death.
- **Low Propensity for Resistance**: The unique mechanism of action is likely not amenable to the easy development of resistance, as it is even difficult to drive resistance to lantibiotics in controlled experiments where resistance to other antibiotics is typically seen.
- **Minimal Cytotoxicity/Immunogenicity**: OG716 has shown limited cytotoxicity *in vitro* in human and mouse cell lines and does not cause an immunological response.

Oragenics is currently completing pre-IND studies with OG716, and we anticipate the company filing an IND with the FDA in the second quarter of 2019 such that clinical trials can be initiate for the treatment of *Clostridium difficile* infection.

INVESTMENT THESIS

Oragenics, Inc. (OGEN) is a biopharmaceutical company developing treatments for oral mucositis (OM) and a novel class of antibiotic compounds known as lantibiotics. AG013 is the company's lead development product for OM and is currently being tested in a Phase 2 clinical trial. OG716 is the company's lead lantibiotic and is being developed for the treatment of *Clostridium difficile* infection.

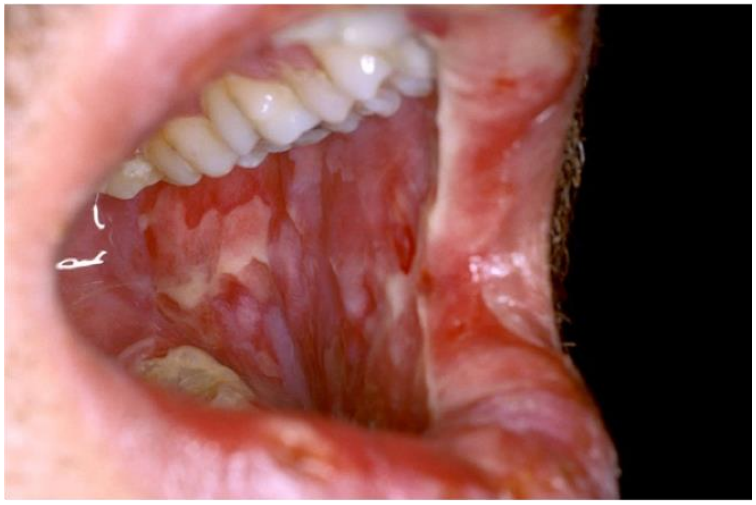


Source: Oragenics, Inc.

AG013

Oral Mucositis

Mucositis is a common and debilitating side effect of cancer chemotherapy and radiation treatment. It results in damage to the epithelial cells that line the gastrointestinal tract and can present as sores and ulcers in the mouth and throat (oral mucositis, OM) or abdominal pain, nausea/vomiting, and diarrhea (gastrointestinal mucositis). OM occurs in approximately 40% of patients receiving chemotherapy treatment, although harsher chemotherapies (e.g., cisplatin, doxorubicin, 5-fluorouracil, etc.) carry a greater risk (Jones *et al*., 2006). The following image shows a patient with severe OM.



Source: myhealth.gov.my

OM is typically graded according to two scales: The World Health Organization's (WHO) Oral Toxicity Scale and the National Cancer Institute's (NCI) Common Toxicity Scale, which are shown below. These tools are composed of four or five-point scales that rate the overall health of the mouth, the severity of patient pain, and the patient's functional capability.

WHO Grading Scale for OM

Grade	Description
0 (none)	None
1 (mild)	Oral soreness, erythema
2 (moderate)	Oral erythema, ulcers, solid diet tolerated
3 (severe)	Oral ulcers, liquid diet only
4 (life-threatening)	Oral alimentation impossible

Source: WHO

NCI Grading Scale for OM

Grade	Description
0 (none)	None
1 (mild)	Painless ulcers, erythema, or mild soreness
2 (moderate)	Painful erythema, edema, or ulcers
3 (severe)	Painful erythema, edema, or ulcers requiring IV hydration
4 (life-threatening)	Severe ulceration requiring nutrional support
5 (death)	Death related to toxicity

Source: Sonis et al., 2004

In addition to degrading a patient's quality of life, severe OM can result in a reduction in a patient's chemotherapy dose or a stoppage in treatment, both of which can lead to a negative clinical outcome, or an increase in infection (Elting *et al*., 2003). There are also serious economic consequences due to the costs associated with symptom management, nutritional support, managing infections, and increased hospital stays. Thus, OM constitutes a serious complication of chemotherapy and radiation treatment.

Treatment of OM

The first evidence-based clinical practice guidelines that discussed care of mucositis were published in 2004 by the Mucositis Study Group of the Multinational Association of Supportive Care in Cancer and International Society of Oral Oncology (MASCC/ISOO) and updated in 2014 (Lalla *et al*., 2014). Treatments are divided into the following categories:

Basic oral care: This consists of debridement and decontamination. Debridement is usually done with a soft-bristle toothbrush to remove the dead tissue. Antifungal and antibacterial mouthwashes are used to prevent infection, however none of those treatments have been shown to reduce the risk of developing OM.

Topical and systemic pain management: Mouth rinses containing lidocaine or morphine along with systemic analgesics are used to control pain. Gelclair® is an FDA approved oral gel that forms a protective film over lesions in the mouth of those suffering from OM. Caphasol® is an FDA approved mouth rinse designed to moisten and lubricate the oral cavity. MuGuard® is an oral wound rinse that forms a protective layer on the mucosal membranes in the mouth.

Prophylaxis: Sucking on ice during administration of bolus 5-fluorouracil or melphalan has been shown to decrease the severity of OM. This is believed to work through vasoconstriction that reduces blood flow to cells in the mouth and limits exposure of those cells to the chemotherapeutic agent.

Kepivance® (palifermin) is a recombinant keratinocyte growth factor that is administered intravenously to decrease the incidence and duration of severe OM for patients receiving myelotoxic therapy prior to autologous hematopoietic stem cell transplant. A study from the early 2000's showed that administration of palifermin for three consecutive days prior to the initiation of conditioning therapy and three consecutive days following transplantation resulted in a statistically significant decrease in the incidence and duration of severe OM (Spielberger *et al*., 2004). The incidence of severe OM (WHO grade 3 or 4) in the palifermin-treated group was 63% compared to 98% in the placebo group (P<0.001). In addition, the median duration of severe OM in the palifermin-treated group was three days compared to nine days in the placebo group (P<0.001).

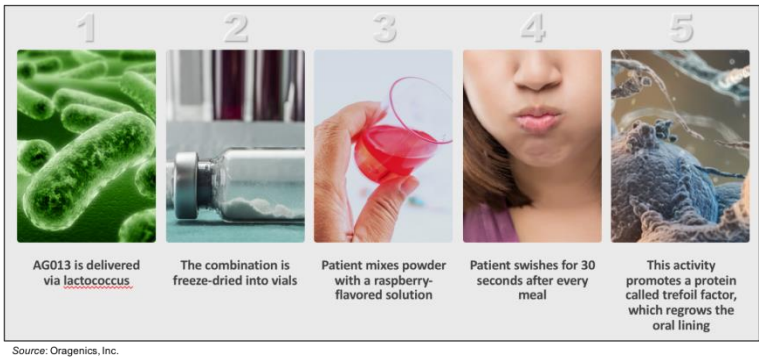
While there are some palliative treatments available to reduce the effects of OM, there does not currently exist an FDA approved therapy for the prevention of OM in a large cancer population. With so many patients affected by the condition, there is clearly a pressing need for more effective treatment and preventative options for OM that target its underlying pathology.

AG013

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).

As opposed to producing a recombinant protein and needing to purify sufficient quantities of it for therapeutic administration, the use of genetically modified *Lactococcus lactis* that secrete a protein or peptide of interest offers an alternative method of biopharmaceutical delivery. In addition, the costs of producing *L. lactis* for therapeutic use are minimal in comparison to producing other types of biotherapeutics such as monoclonal antibodies or purified proteins.

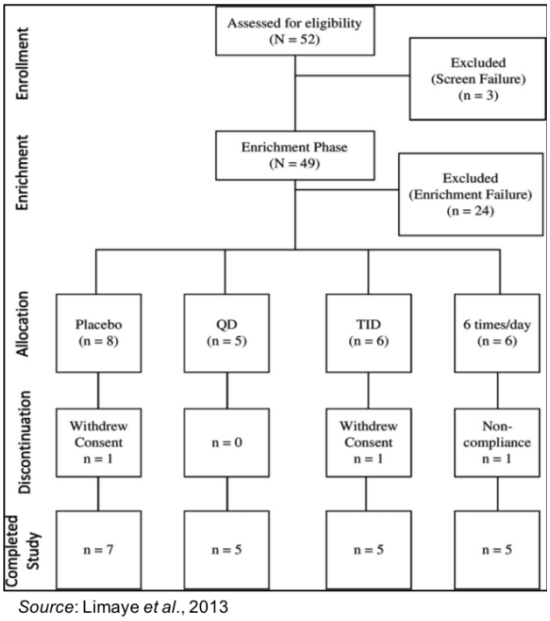
AG013 is an oral mouth rinse composed of a recombinant *L. lactis* strain that contains the coding sequence for human TFF1 (hTFF1), which is continually secreted by the bacteria. The strain lacks the thymidine kinase gene, thus rendering the bacteria unable to replicate without exogenous thymidine administration. Preclinical evaluation of AG013 in a hamster model showed that topical administration of AG013 to the oral mucosa significantly reduced the severity of radiation induced OM, there was no systemic exposure to AG013, and AG013 was unable to survive in the circulation, thus showing it to be a potential safe and efficacious treatment for OM (Caluwaerts *et al*., 2010). The following figure shows the steps involved for using AG013.



Source: Oragenics, Inc.

Phase 1 Trial

In 2012, a Phase 1b, multicenter, single blinded, placebo controlled dose escalating study of AG013 was conducted in patients with newly diagnosed locally advanced head and neck cancer undergoing induction chemotherapy with either TPF (docetaxel, cisplatin, 5-fluorouracil) or PF (cisplatin, 5-fluorouracil) (Limaye *et al*., 2013). Subjects were treated with 15 mL of AG013 or placebo for 1, 3, or 6 times per day. AG013 was formulated at 2.0 x 10^{11} colony-forming units (CFU)/15 mL. An outline of the study is shown below.

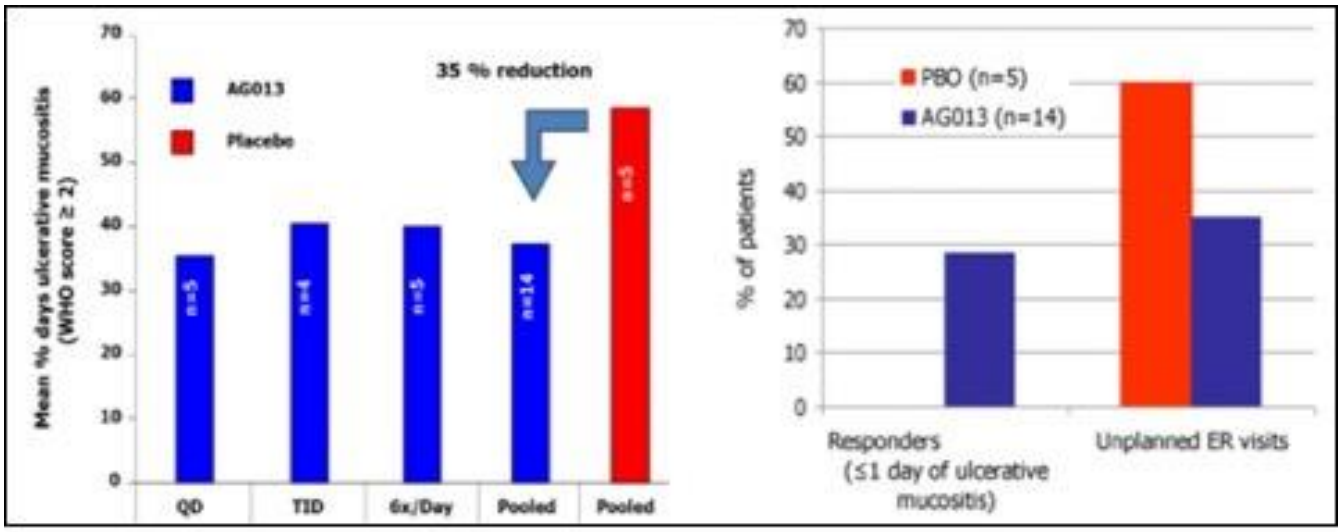


Source: Limaye *et al*., 2013

Subjects who met the eligibility criteria moved on to the enrichment phase where they received the first cycle of chemotherapy and were monitored daily using the Oral Mucositis Daily Questionnaire. Those subjects who experienced mucositis during enrichment proceeded to the active treatment phase where OM was evaluated daily during chemotherapy cycle 2 for days 1-14. A total of 52 subjects were screened, resulting in 49 subjects who met eligibility criteria, and 25 subjects that developed OM during the first course of chemotherapy. 19 of the 25 subjects enrolled in the active phase of the study were included in the efficacy analysis due to two subjects withdrawing consent and four subjects being noncompliant.

Results showed that compliance was highest among the once-daily dosing group (100%) and the 3x/day group (94%), with the 6x/day group having the lowest compliance (62%). Subjects on placebo had an 82% compliance rate. Almost all subjects experienced at least one adverse event (AE) with the most common AE being nausea (11/25, 44%), oral pain (10/25, 40%), fatigue (9/25, 36%), diarrhea (6/25, 24%), and mucosal inflammation (5/25, 20%). Four subjects experienced a severe AE, although none were related to study drug. AG013 bacteria were never detected in the blood of any subject.

Regarding efficacy, the following figure on the left shows that treatment with AG013 resulted in a 35% reduction in the mean percentage of days with ulcerative oral mucositis (UOM) compared to placebo. The following figure on the right shows that 29% of AG013-treated subjects had either 0 or 1 day of UOM while all those on placebo had at least two days of UOM.



Source: Limaye *et al.*, 2013

The Phase 1b trial showed that AG013 can be safely administered to patients receiving chemotherapy and can decrease the severity of OM. An important conclusion from this study was that there is no risk of infection with AG013, as the bacteria did not show up in any treated subjects bloodstream and no there were no reports of sepsis. The bacteria were detectable for approximately 90 minutes following dosing (regardless of how many doses/day were administered) and there was no AG013 detected two weeks following the end of the treatment period.

Phase 2 Trial

To follow up on the results of the Phase 1b trial, Oragenics is currently conducting a Phase 2, double blind, placebo controlled clinical trial of AG013 (NCT03234465). Approximately 160-180 subjects with head and neck cancer receiving chemotherapy will receive either AG013 (2.0×10^{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.

On May 30, 2018, Oragenics announced positive results from an interim safety analysis from 19 patients enrolled in the Phase 2 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. We anticipate study enrollment being completed near the end of 2018 or early 2019 and topline data in mid-2019.

In November 2016, AG013 was granted Fast Track designation by the U.S. FDA. Fast Track designation comes with a number of benefits for Oragenics, including increased interaction with the FDA (including assistance in clinical trial design), a six-month review time for a BLA, and the potential for the Phase 2 study to be considered one of the two required pivotal trials. AG013 has also been granted Orphan Drug status in the E.U.

Other OM Products in Development

In addition to the products listed previously that are currently used for the treatment of OM, we have identified other products currently in development, including:

- GC4419 (Galera Therapeutics, Inc.) – This is a superoxide dismutase mimetic that helps to reduce the level of superoxide caused by radiation therapy through its conversion to hydrogen peroxide and oxygen. On Dec. 18, 2018, Galera announced positive Phase 2b results showing that GC4419 significantly reduced the duration of severe OM by 92% (*P*=0.024) and reduced the overall incidence of severe OM by 34% (*P*=0.009). The full data set will be presented at the 2018 American Society of Clinical Oncology (ASCO) Annual Meeting in June 2018.

- Briiacidin (Innovation Pharmaceuticals, Inc.) – This is a small molecule defensin mimetic that is thought to decrease inflammation and promote wound healing. On May 9, 2018, Innovation released the final data from a Phase 2 clinical trial of brilacidin in patients with head and neck cancer. Results showed that brilacidin reduced the incidence of severe OM from 60% in placebo treated patients to 43% in brilacidin-treated patients.

- SGX942 (Soligenix Inc.) – This is a fully synthetic, 5-amino acid peptide belonging to a class of molecules known as Innate Defense Regulators that modulate the immune system to promote tissue healing. Soligenix is currently conducting a Phase 3 clinical trial of SGX942 in approximately 190 subjects with oral cancer receiving chemoradiation therapy. Results from the study should be reported in the first half of 2019.

OG716

The Growing Threat of Antibiotic Resistance

The increasing prevalence of antibiotic resistance has created an enormous need for new and more effective antimicrobial therapies. A 2013 report from the Centers for Disease Control (CDC) described the grave consequences that could occur if new medicines are not developed to counteract the problem. In the U.S., approximately two million individuals suffer from a serious infection due to a bacterium that is resistant to one or more antibiotics, with at least 23,000 people dying each year as a result of antibiotic-resistant infections. In fact, methicillin-resistant *Staphylococcus aureus* (MRSA) infections in U.S. hospitals are responsible for more deaths than HIV/AIDS and tuberculosis combined (Klevens *et al*., 2006; Boucher *et al*., 2009).

Antibiotic resistance is something that Sir Alexander Fleming, the discoverer of penicillin, first warned against back in the 1950's. At that time the idea of antibiotic resistance was more theoretical, however since the 1980's the rate of antibiotic resistant strains of bacteria has been growing rapidly. Currently, more than 70% of hospital acquired infections are resistant to at least one of the drugs commonly used to treat them. Antibiotic resistance is fueled by the misuse and overuse of antibiotics in both the clinical and veterinary setting. It is estimated that a total of 23×10^6 kg of antibiotics are used annually in the U.S.; half of which is used for the treatment of disease in people with the other half reserved for agriculture and given to livestock animals (Harrison *et al*., 1998). The widespread use of antibiotics results in the survival and selection for organisms that harbor mechanisms for self-preservation, and with the ability of microorganisms to share genetic material these self-preserving principles are spreading rapidly and leading to an abundance of antibiotic-resistant microbes.

The rise of antibiotic resistance not only affects the ability to fight routine infections, but it also undermines the treatment of infectious diseases in patients with other diseases. A number of medical advancements were possible

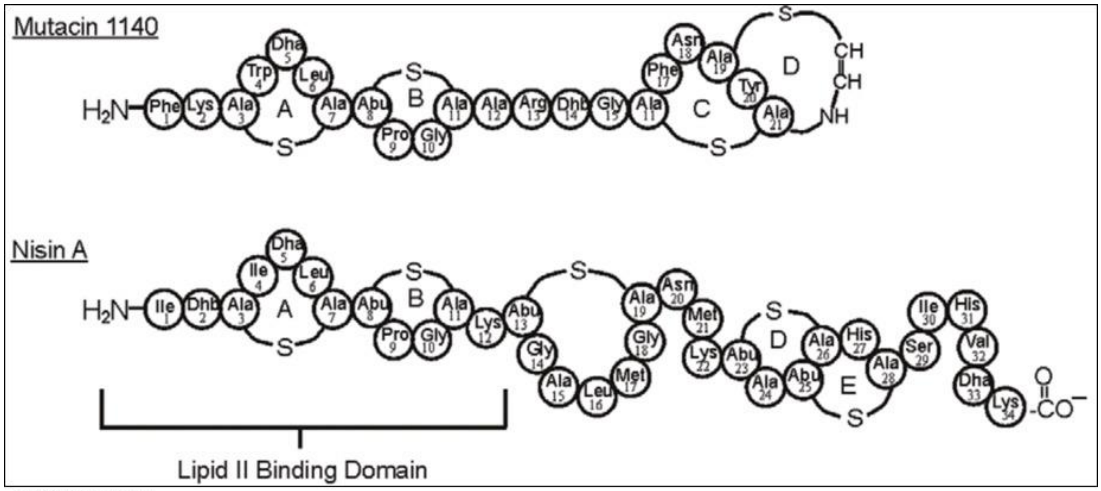
due to the ability to fight infections with antibiotics. These include joint replacements, organ transplants, cancer therapy, and the treatment of various chronic diseases.

The problem of antibiotic resistance isn't limited to just the drug to which an organism develops resistance. Typically, when an organism develops resistance to one member of a class of antibiotics it quickly develops resistance to that entire class. For example, resistance to penicillin quickly gave rise to resistance to all penicillin-like molecules, thus rendering an entire class of compounds ineffective. For this reason, not only are new antibiotics required, but more importantly antibiotics with differentiated mechanisms of action.

Lantibiotics

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).

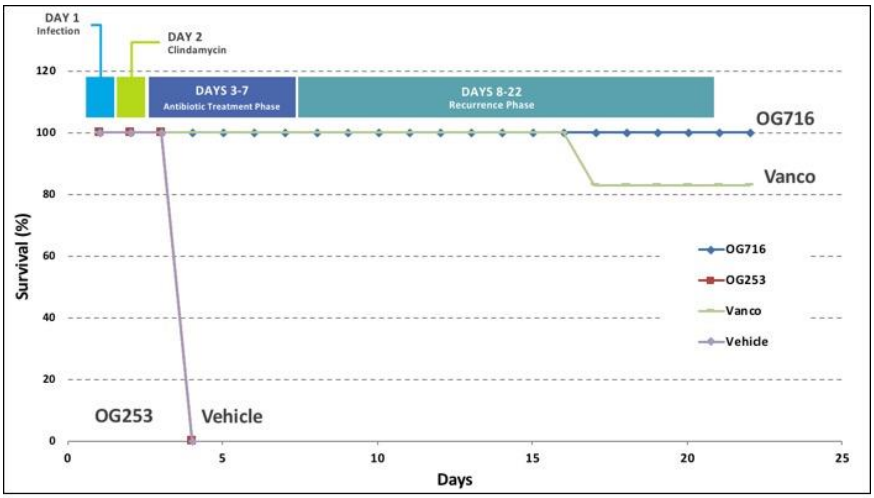
Scientists have been aware of lantibiotics for decades, however they have not been studied as extensively as other classes of antibiotics due to the difficultly in producing sufficient quantities of the compounds. As naturally occurring molecules, lantibiotics are usually produced and secreted into a cells 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, oral 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 that includes single dose-escalating rat studies and 14-day toxicology studies. We anticipate the company filing an IND with the FDA in the second quarter of 2019 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 leads 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.

Intrexon Collaborations

In June 2012, Oragenics entered into the Lantibiotic Exclusive Channel Collaboration agreement with Intrexon Corp. (XON) for the development of mutacin 1140 and related homologs using Intrexon's transgene and cell engineering platforms. In November 2017, the agreement was amended such that the company will owe a single milestone payment of $25 million to Intrexon that is payable within six months of the first regulatory approval of an NDA or BLA. In addition, the royalty rate is now 10% of net sales and Intrexon will spend at least $1.2 million the advance the lantibiotic program in 2018. Lastly, it changed the sublicense revenue split percentage from 50% to 25% for Intrexon. The agreement grants Oragenics an exclusive worldwide license to use patents and other intellectual property of Intrexon in the development of lantibiotic drug candidates.

In June 2015, Oragenics entered into an Exclusive Channel Collaboration agreement with Intrexon whereby the company obtained exclusive rights to AG013 as a potential treatment for OM. According to the agreement, Oragenics will pay a 12% royalty to Intrexon on net sales of AG013. In November 2017, the agreement was amended such that the company will owe a single milestone payment of $27.5 million to Intrexon that is payable within six months of the first regulatory approval of an NDA or BLA. It also changed the sublicense revenue split percentage from 50% to 25% for Intrexon.

Intellectual Property

Oragenics recently announced the U.S. Patent and Trademark Office (USPTO) granted the company and the Texas A&M University System U.S. Patent No. 9,964,488 titled "Variants of the Lantibiotic MU1140 and Other Lantibiotics with Improved Pharmacological Properties and Structural Features". The patent covers both variants of mutacin 1140 as well as their use in treating infections and diseases caused by one or more types of bacteria.

Financials and Capital Structure

As of March 31, 2018, Oragenics reported approximately $4.8 million in cash and cash equivalents. On April 6, 2018, the Company announced pricing for a registered direct offering in which 900,000 shares of common stock were sold at a price of $2.00 per share for total gross proceeds of $1.8 million. Included in the offering were an equivalent number of warrants with an exercise price of $2.00 per share. Cash burn for the first quarter of 2018 was approximately $1.4 million.

Following the April financing, the company has approximately 6.1 million shares outstanding. In addition, there are 12 million shares of Series A Preferred stock outstanding (which are convertible into 1.2 million shares of common stock) and 6.6 million shares of Series B Preferred stock outstanding (which are convertible into 1.32 million shars of common stock). In November 2017, Oragenics issued $3.4 million in equity to Intrexon Corp. in the form of 100 shares of Series C Preferred stock, which pay dividends at an annual rate of 12% through the issuance of additional shares of Series C Preferred stock. In January 2018, the company paid a dividend of 1.733 shares of Series C Preferred stock to Intrexon. The stated value of the Series C Preferred stock is $33,847.9874 per share. When factoring in the approximately 261,000 stock options and the approximately 2.1 million warrants the company has a fully diluted share count of approximately 11.9 million.

Risks to Consider

Oragenics' drug candidates are in the early stages of development: Currently, AG013 is furthest along in development as it is being tested in a Phase 2 clinical trial. Topline results of that trial are likely to be reported in the second quarter of 2019. While Oragenics has previously announced Positive Phase 1b data for AG013 in the treatment of OM, there is no guarantee that these results will be replicated in the Phase 2 clinical trial. If the company is unable to show efficacy in treating or preventing OM in the Phase 2 trial, or if there are new adverse events that were previously unseen in the Phase 1 trial, the company may have to cease development of AG013, which would have a significantly negative impact on the company's share price.

OG716 is still in preclinical development and we anticipate the company filing an IND to initiate a clinical trial in the second quarter of 2019. Even if successful in clinical testing, the drug is still many years away from potentially being approved.

It may be difficult to produce large-scale commercial quantities of OG716. Prior to the mid-2000's, research into lantibiotics was difficult due to the inability to produce sufficient quantities of the drugs for analysis. Oragenics has devised a methodology for producing sufficient amounts of lantibiotic compounds for nonclinical studies. The production of lantibiotics is a highly technical and complex process, and there is no guarantee that the currently used methodology will be amenable to producing commercial-scale quantities of the drugs.

Oragenics will need to raise additional capital in 2018: The company exited the first quarter of 2018 with approximately $4.8 million in cash and cash equivalents. Subsequent to the end of the quarter the company raised gross proceeds of $1.8 million, however that is likely only enough to fund operations through the end of 2018.

MANAGEMENT PROFILES

Alan Joslyn, PhD – President and Chief Executive Officer
Dr. Joslyn was a partner in Lazarus Pharmaceuticals. Prior to that he served as the Chief Executive Officer and Director of several privately held companies including Edusa Pharmaceuticals and Sentinella Pharmaceuticals and prior to that he was the Senior Vice-President Research and Development of Penwest Pharmaceuticals and also held senior drug development positions with Johnson & Johnson.

Michael Sullivan – Chief Financial Officer
Mr. Sullivan has served as Oragenics interim principal executive officer since October 30, 2014 and served as the Chief Financial Officer, Secretary and Treasurer since February 6, 2012. Mr. Sullivan has held senior level financial positions for several publicly and privately held businesses including Utek Corporation, eANGLER, and HSN Direct International Limited. Most recently, he was the Group Financial Officer for the Investigative Services and Litigation Consulting Services segment of First Advantage Corporation. Mr. Sullivan is a Florida Certified Public Accountant. He graduated from the Florida State University with a Bachelor of Science in Accounting and a Master of Business Administration.

Martin Handfield, PhD – Senior Vice President of Discovery Research
Dr. Handfield is the Senior Vice President of Discovery Research and previously has served as the Director of Research and Development. Prior to joining Oragenics, Dr. Handfield held a position as Tenured Associate Professor at the Center for Molecular Microbiology and the Department of Oral Biology at the University of Florida College of Dentistry, where he co-invented IVIAT and co-founded ivi Gene Corp. and Epicure Corp. to commercialize this and related technologies. Dr. Handfield holds a B.S. degree in Biochemistry, and a MS degree and PhD in Microbiology and Immunology from the Université Laval College of Medicine in Canada. He performed postdoctoral training at the University of Florida.

VALUATION

We are initiating coverage of Oragenics, Inc. with a $7.00 valuation. Oragenics is a biopharmaceutical company developing a new treatment for oral mucositis (OM) and a novel class of antibiotics. The company's lead product, AG013, is a novel approach to treating OM that utilizes a mouthwash containing genetically engineered bacteria that secrete human trefoil factor family 1 (hTFF1), which helps to regenerate epithelial cells of the gastrointestinal tract. The company is also developing a new class of antibiotic molecules known as lantibiotics, with the lead development product (OG716) being targeted for the treatment of *Clostridium difficile* infection.

AG013

AG013 is an oral mouth rinse composed of a recombinant *Lactococcus lactis* strain that contains the coding sequence for hTFF1, which is continually secreted by the bacteria. The strain lacks the thymidine kinase gene, thus rendering the bacteria unable to replicate without exogenous thymidine administration. Preclinical evaluation of AG013 in a hamster model showed that topical administration of AG013 to the oral mucosa significantly reduced the severity of radiation induced OM and there was no systemic exposure to AG013.

The company is currently conducting a Phase 2 clinical trial in approximately 160-180 patients with head and neck cancer to test whether AG013 can reduce the incidence and severity of OM. An interim safety analysis showed that AG013 treatment did not lead to any increase in adverse events and there were no reports of sepsis or bacteremia. In addition, the fact that only a few patients have discontinued due to the development of severe OM could be an early sign of efficacy.

With approximately 700,000 cancer patients that develop OM each year and few effective treatment options on the market (and none that prevent the condition in a large patient population), AG013 is set to enter a large market that we estimate could potentially lead to sales of over $200 million.

OG716

Antibiotic resistance continues to be a growing threat all around the world and there is a desperate need for novel classes of anti-infective medicines. Lantibiotics are a novel class of antibiotics that were discovered around the same time as penicillin, however the difficulty in producing enough of the drugs for characterization and study prevented their commercial development. Oragenics has devised a methodology whereby sufficient quantities of these compounds can be produced for use in clinical trials.

Lantibiotics are highly efficacious against a wide range of Gram-positive bacteria, and Oragenics is focusing its lead lantibiotic compound OG716 on the treatment of *C. difficile* infection. The CDC has designated the threat posed by *C. difficile* as Urgent, and with approximately 500,000 infections every year and 29,000 deaths there is a serious need for more treatment options.

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 early 2020, an NDA filing in 2021, and approval in 2022 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 2022, and approval in 2023.

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 $199 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 $15 million.

Combining the net present values for AG013 and OG716 along with the company's current cash position and potential cash from warrant exercises leads to a net present value for the company of $223 million. Dividing by the fully diluted share count of 11.9 million plus an additional 20 million shares to account for future financings leads to a current value of $7.00 per share.

PROJECTED FINANCIALS

Oragenics, Inc.	2017 A	Q1 A	Q2 E	Q3 E	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	$1.5	$1.5	$1.6	$5.9	$6.0	$6.4
General & Administrative	$3.2	$0.8	$1.0	$1.0	$1.0	$3.8	$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)	($2.5)	($2.5)	($2.6)	($9.7)	($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)	($2.5)	($2.5)	($2.6)	($9.7)	($10.0)	($10.4)
Income Taxes	$0	$0	$0	$0	$0	$0	$0	$0
Net Income	($6.7)	($2.1)	($2.5)	($2.5)	($2.6)	($9.7)	($10.0)	($10.4)
Net Margin	-	-	-	-	-	-	-	-
Reported EPS	**($1.37)**	**($0.42)**	**($0.45)**	**($0.41)**	**($0.37)**	**($1.64)**	**($1.00)**	**($0.80)**
YOY Growth	-	-	-	-	-	*20%*	*-39%*	*-20%*
Basic Shares Outstanding	4.9	5.0	5.5	6.1	7.0	5.9	10.0	13.0

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

HISTORICAL STOCK PRICE

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