Zacks Small-Cap Research

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Antibe Therapeutics Inc.

V.ATE - TSX

V.ATE: Initiating Coverage of Antibe Therapeutics Inc.; Developing Next Generation NSAIDs Complemented By Tissue Regeneration Subsidiary…

Based on our probability adjusted DCF model that takes into account potential future revenues from ATB-346 along with Citagenix Inc., ATE.V is valued at CAD$1.25 per share. This model is highly dependent upon continued clinical success of ATB-346 along with the global growth strategy for Citagenix and will be adjusted accordingly based upon future clinical results and the company's execution.

Current Price (03/22/2017)	CAD$0.19
Valuation	**CAD$1.25**

INITIATION

Antibe Therapeutics, Inc. is a Canadian biotechnology company with two diversified business units. The company's lead compound, ATB-346, is being developed as a safer non-steroidal anti-inflammatory drug (NSAID) for treating pain and chronic inflammation. Antibe's subsidiary, Citagenix Inc., is a leader in Canada in the sales and marketing of tissue regenerative products for oral and maxillofacial surgery.

Antibe will be initiating two Phase 2 clinical trials with ATB-346 to support potential partnering with a larger pharmaceutical company. Citagenix is the market leader in dental regenerative medicine in Canada and will be executing a strategic growth initiative in the U.S., which should lead to considerable growth in sales and profitability.

SUMMARY DATA

52-Week High	**$0.28**
52-Week Low	**$0.10**
One-Year Return (%)	**46.43**
Beta	**-1.40**
Average Daily Volume (sh)	**101,493**
Shares Outstanding (mil)	**112.37**
Market Capitalization ($mil)	**$21**
Short Interest Ratio (days)	**N/A**
Institutional Ownership (%)	**N/A**
Insider Ownership (%)	**N/A**
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 #Lin Estimate	**N/A**
P/E using #Lin Estimate	**N/A**

Risk Level	**N/A**
Type of Stock	**Large-Growth**
Industry	**Med-Biomed/Gene**

ZACKS ESTIMATES

Revenue

(In millions of CAD$)

	Q1 (Jun)	Q2 (Sep)	Q3 (Dec)	Q4 (Mar)	Year (Mar)
2016	0.0 A	0.0 A	0.0 A	0.0 A	4.4 A
2017	2.6 A	2.2 A	2.0 A	2.5 E	9.2 E
2018					12.0 E
2019					15.0 E

Earnings per Share

(EPS is operating earnings before non-recurring items)

	Q1 (Jun)	Q2 (Sep)	Q3 (Dec)	Q4 (Mar)	Year (Mar)
2015	-$0.01 A	-$0.01 A	-$0.01 A	-$0.01 A	-$0.04 A
2016	-$0.01 A	-$0.01 A	-$0.02 A	-$0.01 E	-$0.06 E
2017					-$0.04 E
2018					-$0.01 E

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WHAT'S NEW

Initiating Coverage

We are initiating coverage of Antibe Therapeutics Inc. with a CAD$1.25 valuation. Antibe is a Canadian biotechnology company with two diversified business units: one in pain and inflammation and the other in regenerative medicine. The company's lead product, ATB-346, is a next-generation non-steroidal anti-inflammatory drug (NSAID) that is designed to offer the same anti-inflammatory properties of current NSAIDs but with a greatly decreased risk of gastrointestinal side effects. Antibe's subsidiary, Citagenix Inc., is the leading seller of tissue regenerative products for oral and maxillofacial surgery in Canada and recently initiated a strategic growth initiative in the U.S., which should lead to considerable growth in sales and profitability.

Lead Drug is a Potential Game Changer in the Safe Treatment of Pain & Inflammation
ATB-346 is a combination of a hydrogen sulfide (H_2S) releasing moiety with naproxen, a widely used NSAID. Studies conducted thus far have shown ATB-346 to have a number of positive attributes, including:

- **No gastrointestinal damage (GI) in healthy or unhealthy animals**. NSAIDs are known to contribute to an increased risk of GI ulcers. Pre-clinical results with ATB-346 show that the compound is associated with both a decreased propensity for GI injury, but can also promote the healing of GI ulcers that have already formed.
- **Anti-inflammatory effects that are equal to or greater than those of naproxen**. A recent Phase 2 clinical study demonstrated excellent efficacy in humans, with ATB-346 showing pain relief nearly double that of naproxen and celecoxib based on comparable studies.
- **No effect on blood pressure, which is a good indicator of cardiovascular safety**. As opposed to currently available NSAIDs that are known to raise blood pressure, results from Phase 1 and 2 clinical trials show that ATB-346 does not significantly elevate mean arterial blood pressure.

Near-term Milestones including Phase 2 Proof-of-Concept Data this Year
Antibe will be initiating its Phase 2 proof-of-concept GI safety clinical trial in 2Q17 with data before the end of 2017, followed by the initiation of a Phase 2 dose-ranging effectiveness trial to support a potential partnering opportunity with a larger pharmaceutical company. We anticipate the two trials taking approximately 18 months to complete at a cost of approximately $4.5 million, at which time the company will be looking to partner for Phase 3 studies.

Non-Dilutive, Regional Licensing Strategy Supports Funding of Clinical Trials
Antibe recently signed a regional distribution agreement for ATB-346 with Laboratories Acbel SA, a subsidiary of one of Greece's largest pharmaceutical companies, which included an upfront payment of CAD$1.1 million and 5% royalty on net sales. The company continues to negotiate regional distribution agreements for smaller markets (those outside the U.S. and E.U.) in order to generate non-dilutive capital to fund the upcoming Phase 2 studies. Acbel, through its affiliates and partners, is the largest seller of naproxen in this region, which represents approximately 1% of the global market for NSAIDs. Not including the royalty, this transaction effectively values the ATB-346 program at $110 million.

Drug Pipeline Has Blockbuster Potential – Addressing A $9 Billion Global Market Opportunity
NSAIDs comprise one of the largest drug classes worldwide, with estimated sales of both prescription and non-prescription drugs approaching $9 billion in 2016 (EvaluatePharma). Leading prescription NSAIDs include Celebrex® (celecoxib), for which Pfizer reported total revenues of $733 million in 2016 (EvaluatePharma), and Voltaren® (diclofenac), for which Novartis reported total revenues of $525 million in 2016 (EvaluatePharma). The top over-the-counter NSAID products include Advil® (ibuprofen) and Aleve® (naproxen).

Commercial Division in Regenerative Medicine Poised for Global Growth
Citagenix represents Antibe's diversification strategy to augment the high-risk nature of drug development. Citagenix currently operates in 15 countries, including in Canada, where it is the market leader in sales of regenerative tissue products for oral and maxillofacial surgery, through a direct sales force and internationally through a network of distributor partnerships. By leveraging its market leading position in Canada, Citagenix is looking to expand through a global growth strategy that includes strengthening its presence in the U.S. market, which was valued at $341 million in 2014 (iData Research).

INVESTMENT THESIS

Antibe Therapeutics Inc. (ATE.V) is a Canadian biotechnology company developing treatments for pain, inflammation, and regenerative medicine. The company's lead compound, ATB-346, is an improved non-steroidal anti-inflammatory drug (NSAID) that attempts to overcome the well-known and serious side effects of that class of compounds, including ulcers and bleeding in the gastrointestinal (GI) tract. Antibe has successfully completed a series of Phase 1 and 2 clinical trials for ATB-346 and will soon be initiating two Phase 2 clinical trials that will support a potential partnering opportunity with a larger pharmaceutical company.

The company is complementing the high-risk nature of the drug development process with its subsidiary Citagenix, a low-risk, revenue generating entity that is the leader in Canada in the sales and marketing of tissue regenerative products for primarily the dental market.

NSAIDs

NSAIDs are a class of drugs that provide analgesic (pain-reducing) and antipyretic (fever reducing) effects. The non-steroidal portion of the name is utilized to distinguish the drugs from steroids, which have a similar mechanism of anti-inflammatory action.

The mechanism through which NSAIDs exert their effect is through the inhibition of the cyclooxygenase enzymes (COX-1 and COX-2). The COX enzymes are responsible for the production of important biological signaling molecules known as prostanoids, which include prostaglandins, prostacyclin, and thromboxane. Inhibiting the production of these molecules results in reduced inflammation and pain.

There are a number of NSAIDs available both over the counter and as prescriptions, with the difference typically being the dosage strength. Examples of NSAIDs are celecoxib (Celebrex®), ibuprofen (Advil®), and naproxen (Aleve®). The compounds can be administered either orally or topically. When administered orally, NSAIDs are effective in reducing pain and decreasing inflammation; however, they have well documented side effects related to systemic administration.

NSAID side effects

The dose-related GI side effects associated with NSAIDs are a result of the inhibition of the COX-1 enzyme, which is responsible for the normal gastro-protective processes (Roth, 1988). In addition, many NSAIDs are acidic molecules, resulting in irritation to the gastric mucosa. Dyspepsia, abdominal pain, and nausea are all common side effects of oral NSAIDs (Makris *et al*., 2010). While these adverse events are manageable, more serious events are known to occur with oral NSAID use including upper GI bleeding, ulcers, and death (Hernández-Díaz *et al*., 2000).

According to The Arthritis, Rheumatism, and Aging Medical Information System, more than 100,000 Americans are hospitalized each year and more than 16,000 die from ulcers and GI bleeding linked to NSAID use. To limit the gastric side effects, NSAIDs are commonly taken along with a proton pump inhibitor (PPI), such as omeprazole or esomeprazole, that work to limit the amount of acid in the stomach.

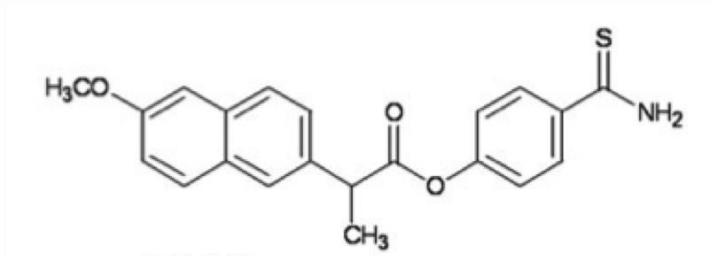
With the discovery of COX-2, research and development efforts were directed at discovering compounds that inhibited COX-2 selectively in order to overcome the GI side effects. While COX-1 is constitutively expressed throughout the body, COX-2 is typically only expressed in inflammation, with the inhibition of COX-2 resulting in the desired clinical response of NSAIDs.

Selective COX-2 inhibitors, such as rofecoxib (Vioxx®), celecoxib (Celebrex®), and valdecoxib (Bextra®), were initially very popular with both physicians and patients for their ability to relieve pain with a significantly decreased risk of adverse GI events. For example, Vioxx achieved over $1 billion in sales in its first year on the market. However, some clinical trials of the COX-2 inhibitors showed that treatment led to an increased risk of adverse cardiovascular (CV) events (Antman *et al*., 2007; Kearney *et al*., 2006). These results led Merck to voluntarily recall Vioxx® in 2004, with Bextra® withdrawn from the market in 2005. In addition, the FDA required a black box warning on the label for Celebrex®.

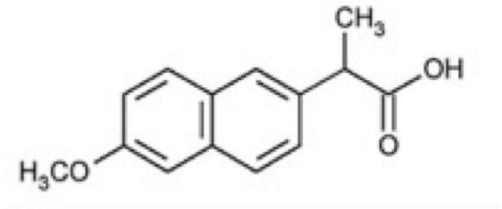
So while on the one hand non-selective NSAIDs are great at offering pain relief, they are accompanied by the threat of serious GI problems, including the development of intestinal damage and bleeding ulcers. Selective NSAIDs are very effective at mitigating pain and they cause significantly fewer GI effects, but they come with an increased risk of CV events. Thus, what is needed is an effective NSAID that does not increase a patient's risk of serious GI or CV events.

ATB-346

Antibe is developing ATB-346 as a solution to the aforementioned problems with NSAIDs. ATB-346 uses naproxen as a base molecule with a hydrogen sulfide releasing moiety covalently attached. Hydrogen sulfide (H_2S) has been identified as an important gasotransmitter, a gas that serves as an important signaling molecule in the body. Other examples of gasotransmitters are nitric oxide (NO) and carbon monoxide (CO).



ATB-346



Naproxen

Hydrogen sulfide's role in the body

H_2S is most commonly known for its very foul odor and potent toxicity, however it is capable of affecting all parts of the body. Recent research has uncovered an important role for H_2S in a variety of biological processes and systems. Endogenous production of H_2S is driven by two enzymes, cystathione β-synthase and cystathione γ-lyase, that utilize L-cysteine as the main substrate (Wang, 2002). These enzymes are expressed in liver, kidney, brain, and lymphocytes. H_2S can also be synthesized from the nonenzymatic reduction of elemental sulfur using reducing equivalents derived from glucose oxidation (Searcy *et al*., 1998).

H_2S has been identified as the third gasotransmitter after NO and CO. NO is the most studied of the three as it plays a large role in cardiovascular functions. The fundamental role of NO is to relax blood vessels and thus lower blood pressure. For this reason, several NO releasing molecules are being developed for therapeutic purposes (Martelli *et al*., 2006). H_2S appears to have similar beneficial cardiovascular effects as NO, with the difference between the two being that NO produces Reactive Oxygen Species (ROS) while H_2S is an ROS scavenger (Martelli *et al*., 2012).

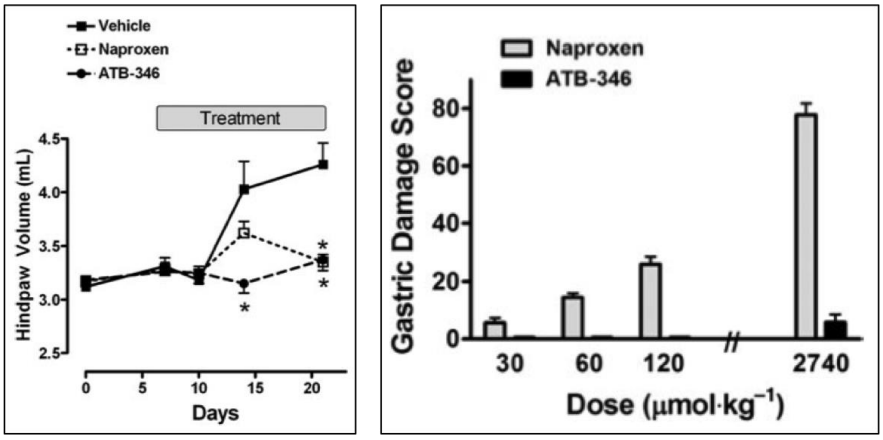
In addition to neutralizing ROS, H_2S activates adenosine triphosphase (ATP)-sensitive potassium channels (K_{ATP}). These channels regulate a number of biological functions in several types of tissues including smooth muscle cells, pancreatic beta cells, neurons, and myocardial cells (Ashcroft *et al*., 1990). Importantly, the level of H_2S appears to be affected by many commonly used drugs, including NSAIDs, which have an inhibitory effect on the production of H_2S in the gastrointestinal mucosa (Fiorucci *et al*., 2005). This may in turn contribute to gastric mucosal injury induced by these drugs. Hence, the pharmacological modulation of H_2S could represent a potential therapeutic application.

ATB-346 protects gastric mucosa from NSAID injury

In an effort to augment the negative side effects of NSAIDs, a hydrogen sulfide releasing moiety (4-hydroxythiobenzamide, TBZ) was covalently attached to the NSAID naproxen and tested in different pre-clinical animal models. Naproxen is one of the most widely used NSAIDs, in part due to evidence that its use may be associated with less cardiovascular toxicity than selective COX-2 inhibitors and other NSAIDs (Kearney *et al*.,

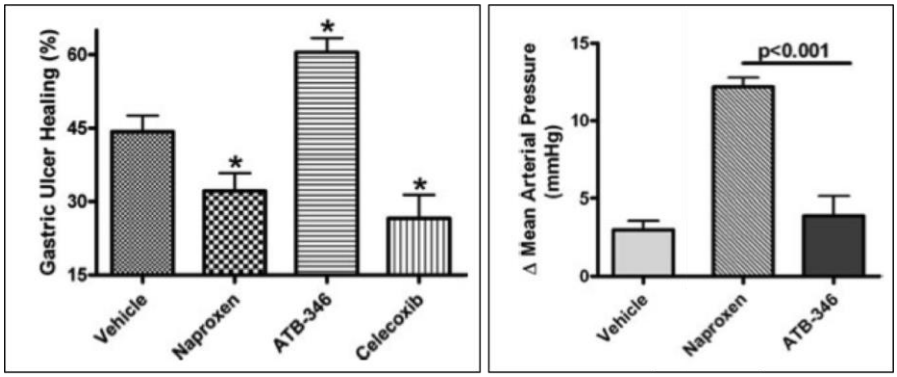
2006). The following studies show ATB-346 to be just as effective as naproxen with a significant reduction in GI toxicity.

- Wallace *et al*., 2010: This study examined the effect of naproxen and ATB-346 in rats by examining a number of different attributes including inflammation alleviation in an arthritis model, gastric damage, and the ability to heal gastric ulcers. The following figure on the left shows that ATB-346 results in a significant reduction in hindpaw inflammation in a rat model of induced arthritis on both days 14 and 21 following arthritis induction, while naproxen only resulted in a significant reduction of swelling on day 21. The figure on the right shows that naproxen results in dose-dependent hemorrhagic damage in the stomach, while ATB-346 showed markedly less damage at all doses tested. At the highest dose tested for ATB-346 (2740 µmol/kg), the compound showed the same gastric damage as that produced by naproxen at 1/100th of that dose (30 µmol/kg). The authors noted that the gastric sparing properties were not evident upon administration of naproxen and TBZ as separate entities.



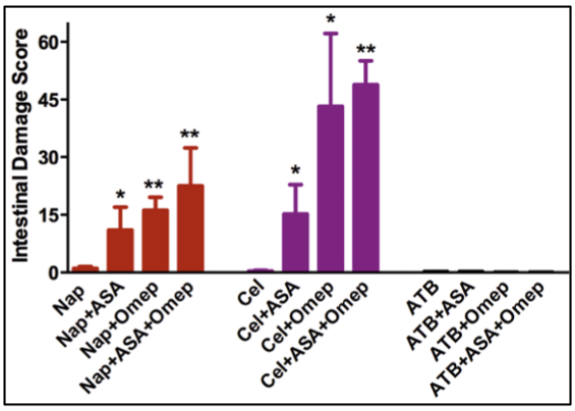
Source: Wallace *et al*., 2010

In addition to promoting the production of ulcers, NSAIDs can interfere with the body's ability to heal pre-existing ulcers. After induction of ulcers in a rodent model, treatment with vehicle resulted in an approximately 50% reduction in the size of the ulcer, as shown in the following figure on the left. Administration of naproxen or celecoxib resulted in significantly less ulcer healing, while treatment with ATB-346 significantly enhanced ulcer healing. Lastly, the following figure on the right shows that administration of ATB-346 did not result in an elevation in arterial blood pressure, while administration of naproxen resulted in a rise above basal blood pressure by ~12 mmHg.



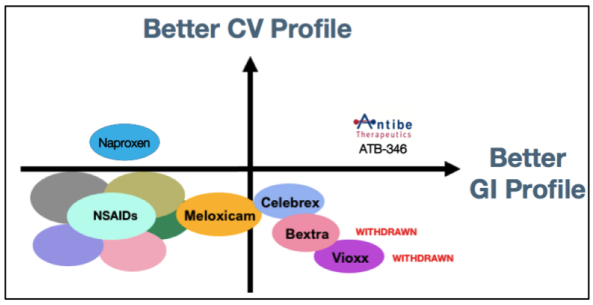
Source: Wallace *et al*., 2010

- Blackler *et al*., 2012: This study examined the effect of celecoxib, naproxen, and ATB-346 in different rat models (arthritic, obese, hypertensive, and aged). Results were very similar to what was reported by Wallace *et al*. in that ATB-346 showed very little to no gastric or intestinal damage in these models. Another model this study looked at was the co-administration of celecoxib, naproxen, and ATB-346 with aspirin and omeprazole (proton pump inhibitor). As the following figure shows, co-administration of both naproxen (Nap) and celecoxib (Cel) with aspirin and omeprazole resulted in increased hemorrhagic injury compared to administration of either drug alone. However, ATB-346 administration with aspirin and/or omeprazole did not result in significant intestinal damage.



Source: Blackler *et al.*, 2012

Based upon the aforementioned pre-clinical data, ATB-346 may ultimately prove to be an efficacious NSAID that has an enhanced GI safety profile and a similar or better CV risk profile. If the pre-clinical data continues to be replicated in clinical testing, ATB-346 could be particularly attractive to patients that are more susceptible to GI damage from traditional NSAIDs, such as the elderly and those with other comorbidities (e.g., diabetes, obesity, etc.).



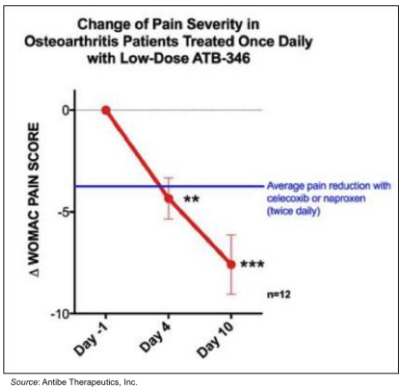
Source: Antibe Therapeutics

ATB-346 Phase 1 Trial

Antibe initiated a Phase 1 trial of ATB-346 in June 2014. On October 6, 2014, Antibe announced the completion of the single ascending dose portion of the trial with the primary objectives of safety and tolerability reached up to the maximum dose tested (1500 mg). However, on January 16, 2015, Antibe announced that it had suspended development of ATB-346 due to safety concerns (liver enzyme elevations in subjects in the highest dose cohort of the multiple ascending dose portion of the study). On March 11, 2015, the company resumed the development of ATB-346 after a thorough review of all Phase 1 data, which suggested a target therapeutic dose of 250 mg or less once daily. Analysis of patient blood samples showed that ATB-346 inhibited cyclooxygenase (COX) at a dose as low as 75 mg and that the inhibition persisted for 24 hours, suggesting once daily dosing would be appropriate. Additional validation studies showed that there was no accumulation of ATB-346 in the liver (or any other organ) and that all metabolites of ATB-346 were rapidly cleared (in rats), further suggesting that toxicity due to lack of metabolism or excretion was not an issue.

ATB-346 Phase 2a Trial

On August 8, 2016, Antibe announced the successful completion of a Phase 2 study of ATB-346 in patients with osteoarthritis of the knee. Twelve patients were treated once daily with 250 mg of ATB-346, which is only 1/6th of the typical daily dose of naproxen for treating osteoarthritis. The patients recorded their pain level one day prior to starting treatment and then again on days 4 and 10 of treatment using the WOMAC pain scale. The graph on the right shows the change in recorded pain level over the 10 days of the study. Previous studies show typical reductions in WOMAC pain scores for osteoarthritis patients taking celecoxib of approximately 4 units following one week of treatment, with no additional improvement beyond that with continued treatment (Wittenberg *et al.*, 2006). Thus, the average reduction of 7.6 units is quite impressive in that study population.



ATB-346 Phase 2b Trials

In order to pursue a global licensing deal with a large multinational pharmaceutical company, Antibe is planning to conduct two Phase 2 clinical trials. The first trial will consist of approximately 250 patients and will involve an examination of endoscopically defined upper GI ulceration in patients taking ATB-346 compared to those taking naproxen over a 2-week period. This study is necessary as the FDA considers endoscopically examining upper GI ulceration the 'gold standard' in assessing NSAID-associated toxicity. Positive results from this study would allow Antibe to pursue a GI safety claim of superiority to naproxen. We anticipate this study initiating in the second quarter of 2017 with results available by the end of 2017.

The second trial will be a placebo-controlled, dose-ranging effectiveness study and consist of approximately 200 patients with osteoarthritis of the knee in order to validate effectiveness and to establish the proper dose for Phase 3 registration studies.

Antibe is currently planning on targeting patients with osteoarthritis, for whom NSAIDs are the most commonly used therapy. Given the risks associated with NSAID use, these patients could benefit greatly from an effective anti-inflammatory/analgesic medication that did not carry the same GI risk. Additional indications for which ATB-346 could be approved include all traditional markets for NSAIDs, including rheumatoid arthritis, ankylosing spondylitis, etc.

Arthritis

Arthritis is inflammation in one or more joints resulting in joint pain and stiffness. The condition typically gets worse with age. There are over 100 different types of arthritis, with the most common form being osteoarthritis. Other forms of arthritis include rheumatoid arthritis, psoriatic arthritis, and septic arthritis.

The most common symptom for all forms of arthritis is varying degrees of pain, swelling, joint stiffness, and occasionally a constant ache around the joint. Other symptoms of arthritis include an inability to use the affected hand or leg, muscle aches, and difficulty moving the affected joint. A 2010 survey by the Centers for Disease Control showed that in the U.S. approximately 50 million adults over the age of 18 had self-reported doctor-diagnosed arthritis (CDC, 2010).

Osteoarthritis

Osteoarthritis (OA) is the most common form of arthritis that affects approximately 250 million adults worldwide (Vos *et al*., 2006). It results in a slow degeneration of the joint through a gradual wearing away of the joint cartilage. It mostly affects weight-bearing joints (e.g., the hips, knees, and ankles) and results in their progressive deterioration. OA affects articular cartilage, which is the smooth, white tissue that covers the ends of bones where they come together to form a joint. Articular cartilage is characterized by a very low friction and a high resistance to wear; however, it also has poor regenerative properties.

There are a number of risk factors for developing OA, which include old age, bone deformities, joint injuries, obesity, and certain diseases such as diabetes, underactive thyroid, or gout. Diagnosis is accomplished through a series of tests that includes a physical examination by a physician along with imaging of the affected joint(s) either radiographically (X-ray) or cross-sectional imaging (magnetic resonance imaging). While there are no blood tests to confirm OA, they are usually performed to rule out other causes of joint pain such as rheumatoid arthritis.

Using 2005 Census data, it was estimated that approximately 27 million people in the U. S. suffered from OA (Lawrence *et al*., 2008). While it has been known to occur in young people, it typically affects those aged 45 and over and is considered as one of the leading causes of lower limb disabilities among the elderly. In addition, as a result of the major loss of function and, due to how it limits activity, OA can also result in depression and a loss of independence. There is also a considerable socioeconomic burden on societies and families due to disabilities brought about by OA.

As there is no cure for OA, treatment is focused on controlling symptoms and preserving physical function. Even with effective management strategies available, OA is both under-diagnosed and under-treated. This may be due in part to the high co-morbidities associated with OA, with upwards of 90% of OA patients suffering from at least one other chronic condition. OA and cardiovascular disease (CVD) are among the most common dyads seen in clinical practice, with CVD precluding the use of OA therapies – particularly NSAIDs.

If left untreated, most patients manage the pain associated with OA by limiting physical activities that exacerbate the pain, such as walking. This limitation of physical activity can then lead to poorer overall health, a higher risk of CVD and worsening of other chronic conditions.

Treatment of OA

There is no known cure for OA, thus treatment is utilized to alleviate the pain and discomfort associated with the condition. In 2012, the American College of Rheumatology (ACR) published recommendations on the use of nonpharmacologic and pharmacologic therapies for OA of the hand, knee, and hip (Hochberg *et al.*, 2012). The ACR recommends the following treatments:

- Non-pharmacologic therapy: cardiovascular exercise, aquatic exercise, weight reduction, walking aids, braces, acupuncture, surgery

- Pharmacologic therapy: acetaminophen, oral NSAIDs, topical NSAIDs, tramadol, cortisone injections, chondroitin sulfate, glucosamine

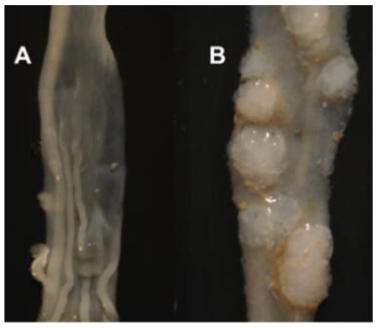
A typical pharmacological treatment regimen begins with the patient starting acetaminophen up to a full dose of 4,000 mg per day. If the patient does not have a satisfactory clinical response, then the health care practitioner is advised to start the patient on oral or topical NSAIDs. As was previously discussed, NSAIDs are known to have adverse GI effects, thus oral NSAIDs are not advised for those > 75 years of age or in those patients with a history or upper GI bleeding. If symptoms continue to persist, tramadol and/or cortisone injections can be utilized. Opioid analgesics are a last resort for patients who have failed all other pharmacological treatments and either cannot or are not willing to go through with joint replacement.

ATB-346 as a Chemopreventative Agent

It is well known that daily aspirin, particularly in patients over the age of 50, can result in significantly reduced occurrence of different GI cancers, including colorectal cancer (Sandler *et al*. 2003). However, just as with other NSAIDs, the use of aspirin is associated with significant GI side effects, thus precluding its recommended daily use for the prevention of cancer. However, given the known effects of H_2S in the GI tract (anti-inflammatory, cytoprotective, and pro-healing), studies have been conducted to examine the use of ATB-346 in the treatment and prevention of colorectal cancer in different animal models.

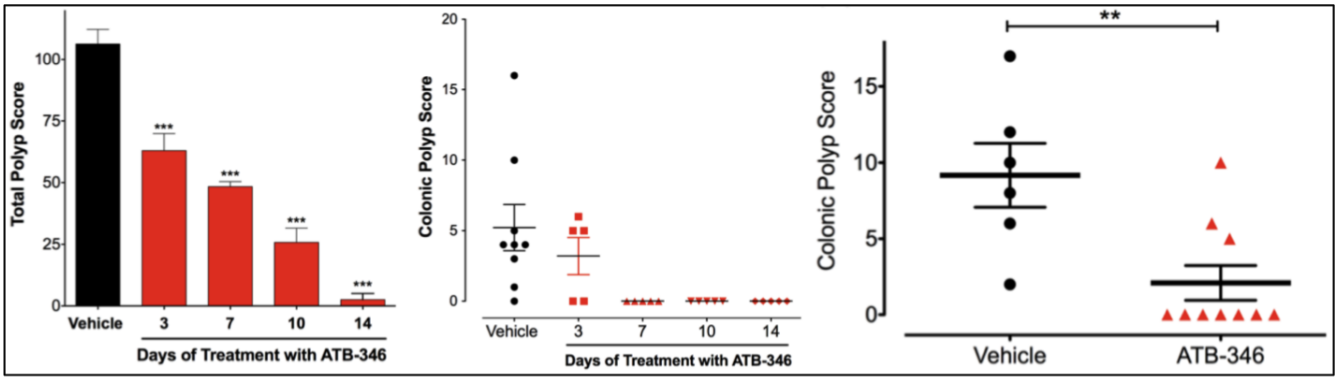
Approximately 70% of spontaneous colorectal cancers involve the inactivation of the Adenomatous Polyposis Coli (APC*)* gene, which is involved in the regulation of epithelial cell proliferation primarily via the Wnt/β-catenin pathway. Those with familial adenomatous polyposis (FAP) suffer from a hereditary form of colon cancer that is linked to mutations in the *APC* gene. The $Apc^{Min/+}$ mouse model mimics FAP, as numerous polyps develop in both the small intestine and colon, and it is widely used to study the effects of various drugs on the development of colorectal cancer (Moser *et al*., 1990).

Paul-Clark *et al*. examined the use of ATB-346 for preventing the formation of polyps in the $Apc^{Min/+}$ model (Paul-Clark *et al*., 2016). The figure on the right shows the ileum from a wild-type mouse (A) and from an $Apc^{Min/+}$ mouse (B), where the presence of polyps is clearly visible in the $Apc^{Min/+}$ mouse.



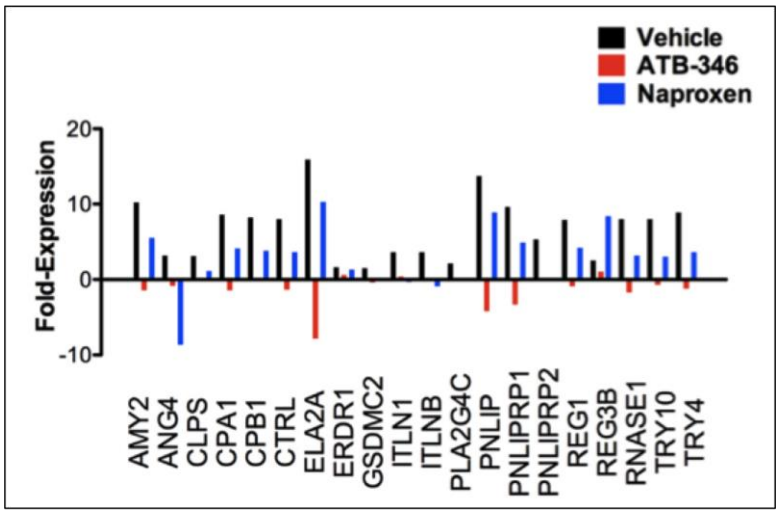
Source: Paul-Clark *et al*., 2016

The use of ATB-346 for 3,7,10, or 14 days during the six and seventh week of life resulted in a dose dependent decrease in the number of polyps seen in $Apc^{Min/+}$ mice following euthanasia of the mice at 14 weeks (lower left). Treatment with ATB-346 for only 7 days during the six and seventh week of life resulted in the complete prevention of colonic polyps (lower middle), while waiting until the 12th week of life (when polyps have already formed) to initiate treatment still resulted in significant resolution, as 70% of mice had no colonic polyps when examined following euthanasia at 14 weeks (lower right).



Source: Paul-Clark *et al*., 2016

Lastly, treatment with ATB-346 resulted in a remarkable effect on gene expression, as shown in the following figure. A total of 19 genes were found to be significantly up-regulated in colon tissue from vehicle treated $Apc^{Min/+}$ mice compared to wild-type mice. Treatment of those mice with ATB-346 completely reversed the over-expression in 18 of the 19 genes. In comparison, treatment with naproxen only reversed the over-expression of 7 of the 19 genes, with a partial effect seen in several others.



Source: Ianaro *et al*., 2016

Antibe is planning to follow up on these initial results with additional preclinical studies, and while the company remains fully focused on developing ATB-346 as an anti-inflammatory/analgesic agent, the potential for its use as a chemopreventative agent could represent significant upside to the story.

Other Pipeline Products

ATB-352: This is a hydrogen sulfide-releasing derivative of ketoprofen, which is a potent NSAID that is normally prescribed for acute pain. Opioids such as oxycontin have a very high propensity for abuse due to being highly addictive, however they are still prescribed at a very high rate as 227 million prescriptions for opioid medications were dispensed in 2015 (IMS Health). In 2014, there were almost 20,000 overdose deaths resulting from the use of prescriptions opioid medications, a 300% increase since 1999 (CDC). Thus, there is an urgent need for a non-addictive acute pain reliever. Antibe recently confirmed that ATB-352 is non-addictive and preclinical data indicates that it results in negligible GI damage compared to ketoprofen. The company initiated toxicology studies in early 2017.

ATB-340: This is a hydrogen sulfide-releasing derivative of low-dose aspirin, which is widely prescribed for the secondary prevention of heart attack and stroke. In addition, low-dose aspirin has shown efficacy in preventing a number of cancers, particularly of the GI tract. However, just as with other NSAIDs, aspirin use is associated with the development of stomach ulcers and GI bleeding. Preclinical results show that ATB-340 caused negligible GI damage compared to low-dose aspirin.

Citagenix

Antibe's subsidiary, Citagenix, is a leader in Canada in the sales and marketing of tissue regenerative products serving the orthopedic and dental markets. Citagenix was founded in 1997, and since that time it has built up a comprehensive portfolio of high-quality, branded biologics and medical devices to promote bone regeneration. The company is currently active in 15 countries, which includes a direct sales staff in Canada and a network of distributor partnerships outside of Canada.

Citagenix's business focuses on three main areas: bone graft substitutes, dental barrier membranes, and surgical instruments.

- **Bone Graft Substitutes**: A bone graft refers to a procedure whereby bone tissue is transplanted in order to promote bone regeneration. Citagenix markets a portfolio of biologics and medical devices that promote bone growth through either osteoconductive (providing a structure to enable blood vessel formation and new bone growth) or osteoinductive (actively recruits surrounding mesenchymal stem cells to become bone-forming osteoblasts via the presence of bone morphogenic protein [BMP]) activity.

- **Dental Barrier Membranes**: These are manufactured from synthetic or biodegradable material and are used in dental surgery to allow bone to regenerate without incursion of surrounding soft tissue. Barrier membranes can be either resorbable (biodegradable) or non-resorbable (synthetic). Resorbable membranes are sourced from animal tissue (e.g., bovine Achilles tendon, porcine small intestine submucosa, etc.) and are absorbed by the body such that no follow-up removal procedure is required. Non-resorbable membranes are commonly made out of titanium-enforced polytetrafluoroethylene (PTFE), and are typically used for procedures that require significant structural support. Resorbable membranes represent approximately 90% of the U.S. market (iData Research Inc.).

- **Surgical Instruments**: BMT Medizintecnik GmbH is a wholly owned subsidiary of Citagenix that designs, manufactures, and markets a portfolio of over 10,000 surgical instruments. All of the instruments are made from martensitic stainless steels (AISI1 421, 440, 440C2) and are sold through BMT's vast distribution network located throughout Europe, the U.S., the Middle East, and Asia. The instruments can be used in a variety of applications, including dental surgery, plastic surgery, general surgery, and by veterinarians.

Antibe is committed to growing Citagenix, which the company views as an important diversification strategy to augment the high-risk involved in the development of ATB-346. In addition, Antibe has the scientific, clinical development, and business development expertise to help Citagenix pursue new opportunities that were previously unavailable due to a lack of adequate resources. Antibe also has access to capital to support the financial commitments necessary for licensing transactions and product development as Citagenix expands into new business opportunities. The company is focused on three core areas in order to grow global market share in the dental regenerative medicine market:

- Antibe will continue to in-license both development-stage and commercial licensing opportunities in order to expand Citagenix's product portfolio. In support of this, last year Antibe in-licensed the Canadian rights for URIST and recently launched PentOS OI™, a suite of bone grafting products that are licensed for Canada and the U.S.
- Antibe is developing two products that target tissue regeneration for use in oral and maxillofacial surgery. Both products are regulated as class I/II medical devices and would be eligible for FDA approval in 12 months or less through a 510(k) registration.
- Antibe is committed to expanding Citagenix's sales, marketing, and distribution capabilities in the U.S. and internationally. The company currently utilizes distribution sales channels in markets outside of Canada, which is viewed as a more cost effective approach compared to a direct sales force. Antibe is exploring acquisition opportunities in order to increase its sales presence in the U.S. as well as developing an e-commerce platform to support sales in North America.

For the last two quarters of fiscal year 2016, Citagenix had $4.4 million in revenue and over the past four quarters the company has generated $9.1 million in revenue.

Intellectual Property

All of the company's intellectual property (IP) regarding NSAID therapeutics is licensed from Antibe Holdings, an IP holding company. Antibe's Chief Scientific Officer, John Wallace, owns 16.7% of Antibe Holdings. The two main patent families cover:

H_2S releasing derivatives of NSAIDs: "Hydrogen Sulfide Derivatives of Non-Steroidal Anti-Inflammatory Drugs"
- U.S. Patents Nos. 7,741,359 and 8,541,398 – expiration 2027

4-hydroxythiobenzamide: "4-Hydroxythiobenzamide Derivatives of Drugs"
- U.S. Patent No. 8,314,140 – expiration 2029

The patent license with Antibe Holdings contains a "4/15" royalty, where Antibe will pay a 4% royalty on net sales or, in the event Antibe sublicenses the IP, a 15% royalty on royalty revenue earned.

Citagenix owns a large portfolio of registered trademarks that are essential for helping to build brand awareness with dental and orthopedic surgeons as part of the company's overall marketing and promotion strategy. The trademarks include: C-Graft Putty™, C-Blast Putty™, Eclipse®, NeoGuarde®, Neomem®, PentOS OI™, and Raptos®.

Financials and Capital Structure

As of December 31, 2016, Antibe had approximately $2.0 million in cash and cash equivalents and a quarterly burn rate of approximately $1.0 million. On February 22, 2017 the company announced a regional licensing agreement with Laboratories Acbel SA for ATB-346 in Albania, Algeria, Bulgaria, Greece, Jordan, Romania, and Serbia. Acbel is a pharmaceutical company with a strong sales and distribution presence in the Balkan region. As part of the agreement, Antibe was issued an upfront payment of approximately $1.1 million and is entitled to receive a 5% royalty on net sales. Given that the territory licensed represents approximately 1% of the global market for NSAIDs, Acbel is valuing ATB-346 at $110 million, not including the royalty. We believe the company has cash to fund operations into the third quarter of 2017.

As of December 31, 2016, the company had approximately 111.7 million common shares outstanding. There are approximately 11.4 million stock options outstanding with a weighted average exercise price of $0.29 along with approximately 33.2 million warrants with an average exercise price of $0.25. Lastly, the company has approximately $3.4 million in convertible debt that can be converted into approximately 15.2 million shares. The fully diluted share count currently stands at 171.5 million shares.

Risks to Consider

Clinical Risk: Antibe suspended clinical development of ATB-346 following the multiple ascending dose clinical Phase 1 clinical trial due to an increase in liver enzymes seen in patients in the higher dosing cohorts. Upon reviewing the data, it was determined that ATB-346 would be effective at much lower doses than animal testing indicated, and upon resuming clinical development a Phase 2 study showed the compound to be effective once daily at 250 mg. There is a possibility that the elevation in liver enzymes could be seen again in the upcoming clinical trials, and if that were to occur it may become more difficult for the company to partner or outlicense the drug. It should be noted that all NSAIDs dose dependently raise these enzymes at high doses.

In addition, the company is pursuing a GI safety claim of superiority to naproxen and while preclinical results have consistently favored ATB-346 over naproxen in regards to GI safety, there is no guarantee that positive results will be seen in clinical trials that involve quantitating endoscopically defined upper GI ulceration.

Development Risk: While the company's stated mission is to get ATB-346 through to the end of Phase 2 testing and then find a larger pharmaceutical partner to finish clinical and regulatory development, there is no guarantee that a suitable partner will be found at under agreeable terms. If a suitable partner were not found, Antibe could develop the drug on its own, however that would require a significant amount of capital and the potential for current shareholders to be significantly diluted.

Financing Risk: The company has yet to be profitable and ATB-346 will require additional capital in order to get through Phase 2 clinical testing, at which point Antibe anticipates entering into a partnership with a larger pharmaceutical company. In addition, Citagenix will require a modest amount of working capital in order to execute on the global growth strategy, which includes supporting its U.S. growth initiative that was launched late last year.

MANAGEMENT PROFILES

Daniel Legault – President and Chief Executive Officer
Mr. Legault is an experienced entrepreneur and executive with extensive experience in guiding early stage businesses in the pharmaceutical, software, consulting and travel industries. Mr. Legault has served as President, CEO and Secretary of Antibe since its formation and he has served as President and CEO of Antibe Holdings since 2005. Mr. Legault previously served as a director and officer of Revelstoke Partners Ltd., a consulting firm providing turnaround services. He has been a principal of Exchange Solutions Inc., a marketing consultancy based in Boston and Toronto, and President of Opal Sky Inc., a Toronto-based marketing software company. Previously, Mr. Legault was President of Butterfield & Robinson Inc., a Toronto-based travel firm, and a Captain in the Canadian Air Force. Mr. Legault was a director and audit committee member of Green Shield Canada (an OSFI-regulated organization) for 17 years, one of the country's largest health benefits administrators. Mr. Legault is a Member of the Law Society of Upper Canada and the New York Bar, and he holds a JD from Queen's University.

Alain Wilson – Chief Financial Officer
Mr. Wilson is a management consultant with extensive experience in strategy and financial analysis in a variety of industries. Over the last 30 years, Mr. Wilson has worked with senior executives on key strategic issues both in North America and internationally. He was a Vice President and Toronto Office Head for Mercer Management Consulting (now Oliver Wyman), and more recently a founding partner of Revelstoke Partners, a boutique consulting firm focused on assisting mid-market companies. Mr. Wilson has a Bachelor of Commerce (Honours) from Queen's University and an MBA from IMD in Switzerland.

John Wallace, PhD – Chief Scientific Officer
Dr. Wallace is an Adjunct Professor of Physiology & Pharmacology at the Faculty of Medicine at the University of Calgary. He holds a PhD in Medical Sciences (University of Toronto), and a B.Sc. and M.Sc. in Biological Sciences (Queen's University). From 2009 to 2012, John was Founding Director of the Farncombe Family Digestive Health Research Institute at McMaster University. He completed post-doctoral studies at the Wellcome Research Laboratories in London, England, and he holds an MBA from the University of Birmingham, England.

David Vaughn, PhD – Chief Development Officer
Dr. Vaughn has over 20 years of experience in the pharmaceutical industry as a drug development consultant providing support for preclinical, clinical, regulatory, business development, and marketing functions in the anti-infectives, central nervous system, and GI disease areas. He is the former head of the anti-infectives product development unit for Bayer Inc. Dr. Vaughn holds a PhD in Clinical Biochemistry from the University of Toronto.

VALUATION

We are initiating coverage of Antibe Therapeutics, Inc. (ATE.V) with a $1.25 valuation. Antibe has two diversified business units: one in pain and inflammation and the other in regenerative medicine. The company's lead product, ATB-346, is a next-generation NSAID that is designed to offer the same anti-inflammatory properties of current NSAIDs but with a greatly decreased risk of gastrointestinal side effects. Antibe's subsidiary, Citagenix Inc., is the leading seller of tissue regenerative products for oral and maxillofacial surgery in Canada and recently initiated a strategic growth initiative in the U.S., which should lead to considerable growth in sales and profitability.

ATB-346

Antibe's lead anti-inflammatory product, ATB-346, uses naproxen as a base molecule with a hydrogen sulfide releasing moiety covalently attached. The compound attempts to overcome the shortcomings of NSAIDs, namely the risk for severe gastrointestinal complications, while still offering the same, or better, pain relief and anti-inflammatory response. Data from Phase 1 and 2 clinical trials showed no issue with increased blood pressure, which is common with currently available NSAIDs, and pain relief that was better than naproxen or celecoxib based on comparable studies.

A Phase 2 study to investigate gastrointestinal safety will be initiated in the second quarter of 2017 with results due before the end of 2017, which could be a major catalyst for the share price. Antibe will also be initiating a second dose-ranging Phase 2 study later in 2017 to investigate the effectiveness of ATB-346 at different dosage strengths. The results from both of these studies will be used to support potential partnerships with a larger pharmaceutical company.

ATB-346 will be entering a NSAID market that is currently valued at almost $9 billion (EvaluatePharma). An effective anti-inflammatory and pain reliever that did not carry the same risks as traditional NSAIDs would likely generate worldwide revenues of at least $1 billion, as Celebrex® (celecoxib) had peak sales of $2.9 billion even with a 'black box' warning regarding an increased risk of cardiovascular events with long-term use.

Citagenix

Due to the high-risks associated with drug development, Antibe acquired Citagenix, which is a revenue generating operation that is currently active in 15 countries. In Canada, Citagenix is the leader in regenerative tissue products for oral and maxillofacial surgery and has attained this position using a direct sales force. In the other countries it operates in, Citagenix uses a network of distributor partnerships. In an effort to expand, Citagenix is looking to expand its presence in the U.S. market, which was valued at $341 million in 2014 (iData Research), and is currently investigating acquisition opportunities in order to increase its sales presence in the U.S. as well as developing an e-commerce platform to support sales in North America. While Citagenix is an important de-risker for Antibe, it does not add considerably to the valuation at this juncture.

Valuation

We value Antibe using a probability adjusted discounted cash flow model that takes into account potential future revenues for ATB-346 and Citagenix. For ATB-346, we anticipate that the company will enter into a collaboration with a larger pharmaceutical company before Phase 3 studies commence. For modeling purposes, we are estimating that Phase 3 studies for ATB-346 will begin in 2019, with an NDA filing in 2020 and approval in 2021. We model for approval in the E.U. a year later.

ATB-346 is the main value driver for Antibe as the NSAID market is valued at $8 billion total. We model for approval in OA, however we believe that if the drug is approved it will likely go on to be approved for multiple indications similar to celecoxib. There are approximately 27 million individuals in the U.S. with OA (NIAMS). Of those, we estimate approximately 50% are taking or are open to taking oral NSAIDs. With a conservatively estimated 6% of the market, ATB-346 would have peak sales of $1.0 billion. In the E.U., where there are approximately 40 million patients with OA (WHO), a similar market share could generate close to $1 billion in revenue. Using a 12% royalty rate, an 18% discount rate, and a 50% chance of approval, we estimate the net present value of ATB-346 to be $171 million. When taking into account estimated capital requirements (~$10 million), the current conversion to Canadian Dollars (USD$1 = CAD$1.34), and dividing by the fully diluted share count of 171 million shares leads to a valuation of approximately CAD$1.25. Antibe is certainly an interesting story and we encourage investors to get familiar with the company ahead of Phase 2 data readouts later in 2017 and 2018.

PROJECTED FINANCIALS

Antibe Therapeutics, Inc.
Income Statement

Antibe Therapeutics, Inc. Fiscal Year Ends Mar. 31 / in Canadian dollars	FY 2016 A	Q1 '17 A	Q2 '17 A	Q3 '17 A	Q4 '17 E	FY 2017 E	FY 2018 E	FY 2019 E
ATB-346 (sales)	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0
ATB-346 (royalty)	**$0.0**	**$0.0**	**$0.0**	**$0.0**	**$0.0**	**$0.0**	**$0.0**	**$0.0**
YOY Growth	-	-	-	-	-	-	*#DIV/0!*	*#DIV/0!*
ATB-352 (sales)	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0
ATB-352 (royalty)	**$0.0**	**$0.0**	**$0.0**	**$0.0**	**$0.0**	**$0.0**	**$0.0**	**$0.0**
YOY Growth	-	-	-	-	-	-	-	*#DIV/0!*
Citagenix	**$4.4**	**$2.6**	**$2.2**	**$2.0**	**$2.5**	**$9.2**	**$12.0**	**$15.0**
Licensing / Development	**$0.0**	**$0.0**	**$0.0**	**$0.0**	**$0.0**	**$0.0**	**$0.0**	**$0.0**
Total Revenues	$4.4	$2.6	$2.2	$2.0	$2.5	$9.2	$12.0	$15.0
YOY Growth	-	*#REF!*	*#REF!*	*#REF!*	*#REF!*	*108.4%*	*29.8%*	*25.0%*
Cost of Goods Sold	$2.4	$1.5	$1.3	$1.1	$1.5	$5.3	$5.8	$6.0
Product Gross Margin	*46.3%*	*43.4%*	*41.4%*	*43.4%*	*42.0%*	*42.5%*	*51.7%*	*60.0%*
SG&A	$5.1	$2.2	$1.9	$2.3	$2.1	$8.5	$8.5	$9.0
% SG&A	*116.0%*	*84.9%*	*85.7%*	*119.4%*	*84.0%*	*92.2%*	*70.8%*	*60.0%*
R&D	$0.4	$0.1	$0.2	$0.2	$0.2	$0.7	$3.5	$1.8
% R&D	*9.2%*	*3.9%*	*10.6%*	*10.5%*	*8.0%*	*8.0%*	*29.2%*	*12.0%*
Operating Income	($3.5)	($1.2)	($1.2)	($1.7)	($1.3)	($5.3)	($5.8)	($1.8)
Operating Margin	*-78.8%*	*-45.5%*	*-54.9%*	*-86.5%*	*-50.0%*	*-57.6%*	*-48.3%*	*-12.0%*
Interest Income / Net	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0		
Pre-Tax Income	($3.5)	($1.2)	($1.2)	($1.7)	($1.2)	($5.3)	($5.8)	($1.8)
Taxes	($1)	$0	($0)	$0	$0	$0	$0	$0
Tax Rate	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*
Net Income	($2.6)	($1.2)	($1.2)	($1.9)	($1.2)	($5.4)	($5.8)	($1.8)
YOY Growth	*#REF!*	-	-	-	-	*107.4%*	*6.5%*	*-69.0%*
Net Margin	*-59.2%*	-	*-53.1%*	*-94.7%*	*-49.9%*	*-58.9%*	*-48.3%*	*-12.0%*
Reported EPS	($0.04)	($0.01)	($0.01)	($0.02)	($0.01)	($0.06)	($0.04)	($0.01)
Fully Diluted Shares	62.7	81.1	93.3	96.1	115.0	96.4	135.0	150.0

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

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