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Biotechnology
Initiating Coverage
September 12, 2019
BUY

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JAGUAR HEALTH, INC.

JAGX: Initiating Coverage with Buy Rating and $5 Price Target

JAGX (NASDAQ)

Company & Market Data	
Closing Price (as of 09/11/2019):	$1.10
Rating:	BUY
Price Target:	$5.00
52 Week Range:	$1.00 - $175.00
Shares Outstanding (MM):	6.1
Market Capitalization (MM):	$7
Cash (MM):	$1.6
Debt (MM):	$11.7
Fiscal Year End:	Dec

Estimates	2018A	2019E	2020E
EPS			
1Q	$(54.27)	$(9.78)A	$(0.54)
2Q	$(53.24)	$(15.11)A	$(0.16)
3Q	$(37.77)	$(0.81)	$(0.17)
4Q	$(42.46)	$(0.76)	$(0.18)
Full Year	$(197.82)	$(5.76)	$(0.81)
Revenue (MM)	$4.2	$7.0	—

Ratios			
P/E	NA	NA	NA

*EPS: Quarters do not add due to changes in shares outstanding.

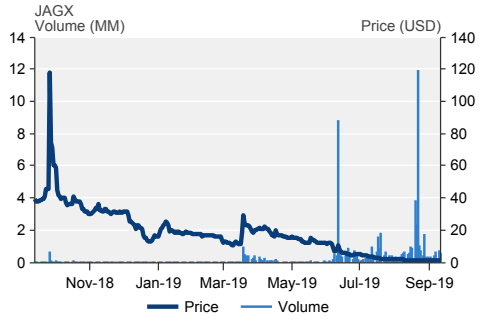


Chart data: Bloomberg

We are initiating coverage of Jaguar Health, Inc. (JAGX) with a Buy rating and price target of $5 per share.

Jaguar is developing crofelemer, its anti-diarrhea drug, for conditions where diarrhea is a serious problem. Crofelemer has a unique anti-secretory mechanism of action that blocks chloride channels in the large intestine. This prevents outflow of chloride and water from the cells to stop the diarrhea, ion imbalance, and dehydration that results. It is not systemically absorbed, has few side effects, and a targeted mechanism of action that distinguishes it from other diarrhea medications.

Clinical Development: The first indication for crofelemer was approved in 2012. It is marketed under the name Mytesi for symptomatic relief of noninfectious diarrhea in adults with HIV/AIDS on antiretroviral therapy, and has established long-term safety with chronic use.

The lead indication in clinical trials is for prophylaxis to prevent diarrhea in patients receiving chemotherapy regimens where diarrhea is a dose limiting side effect. A Phase 2 trial, known as HALT-D, is testing crofelemer in combination with trastuzumab, pertuzumab, and docetaxel. This drug combination has a high incidence of severe diarrhea that can be dose limiting or require ending the treatment. An interim analysis is expected to be announced in 3Q19, with full results in 1Q20.

The company has met with the FDA to plan the Phase 3 trial to file a supplemental NDA and will finalize the protocol based on the Phase 2 results. Crofelemer's existing safety database, its chemical and manufacturing controls, and toxicity studies were all acceptable for the application. We anticipate Phase 3 studies could begin in late 2020.

Additional Indications: Other indications for congenital conditions and conditions associated with debilitating diarrhea are in development. These include congenital diarrhea disease (CDD), short bowel syndrome (SBD), and idiopathic diarrhea.

A second generation version, lechlemer, is in development for cholera and general watery diarrhea. The cholera indication could be eligible for a Tropical Disease Priority Review Voucher (PRV) from the FDA, which shortens review time for an NDA. PRV vouchers can be sold to other companies, with recent sales in the $80 million to $105 million range.

Conclusion and Valuation: We expect JAGX to be driven by the progress of crofelemer in its additional indications. The interim results from the HALT-D study are expected late in 3Q19, followed by the full trial results in 1Q20. These announcements could be the first data showing that crofelemer can make chemotherapy more tolerable and allow the drug regimens to be used more effectively. We would expect this to be seen as proof of concept for other conditions with secretory diarrhea, improving the prospects for crofelemer sales.

We value JAGX based on our 2024 EPS estimate of $1.03, discounted at 30% with a multiple of 15X. Our price target is $5 per share.

Investment Summary

We are initiating coverage of Jaguar Health with a Buy rating and a price target of $5 per share. The company is developing crofelemer, an anti-diarrhea medication with a novel mechanism of action. Crofelemer is currently marketed as Mytesi and was first approved in 2012 to manage the side effects of anti-retroviral therapy drugs used to treat HIV/AIDS. Several clinical trials are in progress for managing diarrhea in several conditions which can be serious enough to require hospitalization and treatment. If these clinical trials are successful, crofelemer could be a novel, effective drug for controlling severe diarrhea.

The lead indication is for chemotherapy regimens where the incidence and severity of diarrhea can require stopping therapy and hospitalizing the patient. Additional indications in other gastrointestinal conditions with severe diarrhea are in progress, including short bowel disease, congenital conditions, and inflammatory bowel diseases. A second-generation version, lechlemer, is in development for cholera and may be eligible for a Tropical Disease Priority Review Voucher.

Product Background

Crofelemer has a different mechanism of action than other anti-diarrheal agents. It is an anti-secretory agent that blocks the chloride channel in the cells of the intestine, preventing water flow out of the cell into the intestinal lumen.

This contrasts with the common anti-motility drug Immodium (loperamide), which slows the movement of material through the intestine to increase water resorption. Other drugs, such as Pepto Bismol and Kaopectate, increase absorption of fluids but have little efficacy in chemotherapy treatment related diarrhea. These drugs are used for short-term diarrhea management, but not for prevention. None have established long-term safety suitable for chronic use. Crofelemer's targeted mechanism of action has shown potential for use in several indications where diarrhea can be severe and cause long-term effects on the patient.

Crofelemer was originally developed by Napo Pharmaceuticals (previously private), which out-licensed the human applications in 2008. The licensee, Salix Pharmaceuticals (Now part of Bausch Health, BHC, $23.10, Not Rated), ran clinical trials and received approval for use in diarrhea associated with HIV/AIDS antiretroviral therapy in 2012. Napo formed Jaguar in 2013 as a subsidiary to develop veterinary indications. In 2016, Napo regained all rights to the human applications and the two companies merged in 2017, bringing both human and animal indications back to a single company. The product was renamed Mytesi, given more marketing support, and moved forward in development for new indications.

Chemotherapy Treatment-Related Diarrhea (CTD) is a dose-limiting toxicity that can require delaying or discontinuing therapy. Several categories of oncology drugs have strong efficacy, but their high incidence of diarrhea prevents them from being used more extensively. The lead clinical trial is testing crofelemer prophylaxis with a chemotherapy combination that has high incidence and severity of diarrhea that can require reducing or stopping treatment, as well as hospitalizations.

Drugs to reduce anemia, neutropenia, and chemotherapy-induced nausea and vomiting (CINV) have made chemotherapy more tolerable and allowed patients to complete their course of therapy without interruption, improving outcomes. These drug categories have become standards of care with annual sales in the multi-billion ranges. If clinical trials are successful, crofelemer could prevent dose-limiting diarrhea in chemotherapy regimens.

Crofelemer could become the first CTD drug, mitigating a problem that prevents use of effective drug regimens.

Recent Developments Have Improved Fundamentals

Jaguar has made several important changes that we believe have improved its long-term outlook. Jaguar merged with its parent company, Napo, bringing the human and animal rights back to a single public company that can direct its resources toward promising indications. Mytesi sales have improved, and the company is focusing on applications where crofelemer can have a significant clinical impact. The company was also able to raise $16.6 million in July 2019 which we estimate will be sufficient to last through important data points in 2020.

The lead clinical trial, known as HALT-D, is using crofelemer for prophylaxis with breast cancer regimen that includes Taxotere (docetaxel), Herceptin (trastuzumab), and Perjeta (pertuzumab). This trial was initiated by an investigator at Georgetown Medical Center who recognized that controlling diarrhea could increase use of the regimen and improve patient outcomes. It is funded by Genentech (part of Roche, RHHBY, $34.00, Not Rated), the maker of Herceptin and Perjeta. An announcement of interim analysis results is expected in late 3Q19, with full results expected in 1Q20.

In March 2019, Jaguar held discussions with the FDA for design of Phase 3 studies for label expansion. Importantly, use of crofelemer (Mytesi) in HIV/AIDS has established a database showing its safety for long-term chronic use. No other safety trials or toxicity studies are required. We expect the company to finalize the Phase 3 trial design after the HALT-D interim analysis is presented. It plans to form a partnership for Phase 3 development in 4Q19/1Q20 that would include Phase 3 funding, milestones, and royalties in exchange for marketing rights.

In August 2019, the company reported results from a preclinical study in which animals were treated with a tryrosine kinase inhibitor (TKI) and either crofelemer or placebo. The drug was dosed at 125mg either twice or four times each day. The difference between the combined treatment groups showed significant improvement ($p<0.01$) over the placebo group. Although this was a preclinical animal study, its design was based on the same criteria as the Phase 3 ADVENT approval trial and the upcoming Phase 2 HALT-D trial. We believe these similarities bode well for the HALT-D trial.

Additional Studies Are in Progress

The company has ongoing trials for additional indications where secretory diarrhea can cause secondary complications. These include the rare pediatric disorders such as short bowel syndrome (SBS) and congenital diarrheal disorders, as well as inflammatory bowel disease, and traveler's diarrhea. The Phase 2 trial for congenital diarrhea disease is expected to start in 2H19.

Lechlemer is a second generation version of crofelemer in development. It has the same mechanism of action as crofelemer and is also derived from the sap of the *Croton lechleri* tree but would have a lower cost of manufacturing. Lechlemer is in development for cholera, a gastrointestinal disorder that is estimated to have 3 million to 5 million cases and cause 130,000 deaths each year. Cholera is a tropical disease currently eligible for a priority review voucher (PRV) from the FDA. PRVs are intended to encourage drug development in unmet needs, small populations, or rare conditions. They are awarded after approval and entitle a subsequent new drug application to faster review, allowing the

drug to reach the market sooner. Over the past two years, PRVs have sold for $80 to $150 million, with $105 million as the most recent sale in March 2019.

Conclusion and Valuation

We expect JAGX to be driven by the progress of crofelemer in its additional indications. The interim results from the HALT-D study are expected late in 3Q19, followed by the full trial results in 1Q20. These announcements could be the first data showing that crofelemer can make chemotherapy more tolerable and allow the drug regimens to be used more effectively. We would expect this to be seen as proof of concept for other conditions with secretory diarrhea, improving the prospects for crofelemer clinical trials and sales.

Our revenue estimates are based on the breast cancer indication in the HALT-D trial and general oncology. Successful clinical data in other indications could cause us to revisit our estimates and valuation. We value JAGX based on our 2024 EPS estimate of $1.03, discounted at 30% with a multiple of 15X. Our price target is $5 per share.

Company Background

Many centuries before the modern pharmaceutical industry began, plants were used as therapeutics for common ailments. The first pharmaceutical products were derived from folk remedies or were derived from plants, with aspirin and morphine being two historical examples. More recently, the success of metformin and paclitaxel renewed interest in finding active agents to make drugs from plants. Pharmaceutical companies have analyzed plant extracts from every continent but had little success in the Amazon.

Napo's predecessor, Shaman Pharmaceuticals, explored plant species in the Amazon rain forest. One of its findings was a preparation made from sap of the *croton lechleri* tree that natives used for gastrointestinal illnesses, diarrhea, inflammation, and other ailments.

Napo began its research by following the traditional preparation methods as precisely as possible. In contrast, most pharmaceutical companies used their own methodologies to isolate active compounds then formulate them into commercial-scale pharmaceuticals. Napo's approach included steps that would have been excluded by a trained medicinal chemist. Some of these steps had unexpected results on the final product, allowing Napo's compound to succeed where previous attempts would have failed.

Napo named the compound crofelemer and began preclinical research and development. In 2008, it out-licensed the human health applications to Salix Pharmaceuticals. Salix conducted the Phase 3 ADVENT trial and received FDA approval in 2012 for managing diarrhea in patients with HIV/AIDS taking anti-retroviral therapies. This was intended as a first indication with a fast route-to-market while indications for larger populations were in development.

In 2013, Napo formed Jaguar Animal Health as a wholly-owned subsidiary to develop veterinary applications. Jaguar became a majority owned, independent company in 2014, then went public in May 2015. During this time, Salix went through strategic changes, and did not support the launch with the resources needed or pursue other indications. The drug languished, and Salix was acquired by Valeant Pharmaceuticals (now Bausch Health, BHC, $23.10, Not Rated) in April 2015.

In 2016, Napo reacquired rights to the human applications from Valeant. Jaguar and Napo merged into a single company in July 2017, bringing the human and animal rights back to a single public entity. Jaguar Animal Health changed its name to Jaguar

Health, Inc. with Napo as a wholly-owned subsidiary. The drug was relaunched with a new name, Mytesi, and a new marketing program. The company also changed its focus to develop applications in chemotherapy and gastrointestinal diseases where diarrhea is a serious problem. A second-generation anti-secretory product, lechlemer, is in development for cholera. Animal health programs continue in areas that have applications to humans.

New Trials For Human Applications

Crofelemer is in development with chemotherapy drug combinations that have high incidence and severe diarrhea. There are many cancer drugs that are highly effective but are not used due to the diarrhea they cause. Drugs to manage anemia, neutropenia, and nausea and vomiting from chemotherapy have allowed patients to receive their treatments on schedule without stopping to recover from toxicities. However, diarrhea remains a dose-limiting side effect with no effective treatments. If the clinical trials show improvement, crofelemer could become the first CTD drug and allow increased use of effective chemotherapy drugs.

Exhibit 1: Jaguar Health Pipeline

Product	Indication	Development	Pre-clinical	Phase I	Phase II	Phase III	Marketed
Mytesi	Non-infectious diarrhea in adults receiving HIV/AIDS antiretroviral therapy						
Crofelemer	Cancer therapy-related diarrhea (CTD)						
Crofelemer	Supportive care for IBD						
Crofelemer	Short Bowel Syndrome/Congenital diarrhea disease						
Crofelemer	IBS - Diarrhea predominant (IBD-D)						
Crofelemer	Idiopathic/functional diarrhea						
Lechlemer (Second generation crofelemer)	Cholera and other GI indications						

Source: Jaguar Health, Inc.

Exhibit 2: Upcoming Events

Product	Species	Indication	Event	Timeline
Crofelemer		Chemotherapy treatment-related diarrhea (CTD)	Interim data from Phase 2 study	3Q19
Crofelemer		Idiopathic/functional diarrhea	File IND	3Q19
Canalevia		Chemotherapy induced dirrhea (Dogs)	File Animal Safety section for FDA approval	3Q19
Crofelemer		Congenital bowel syndrome/Short bowel syndrome	File IND for trial in Abu Dhabi	2H19
Crofelemer		Cholera	File IND	2H19
Crofelemer		Chemotherapy treatment-related diarrhea (CTD)	File IND for supplemental indication	2H19
Crofelemer		All	Form partnership agreements	4Q19/1H20
Crofelemer		Chemotherapy treatment-related diarrhea (CTD)	Full data from Phase 2 study	1Q20

Source: Company filings and Ladenburg Thalmann estimates

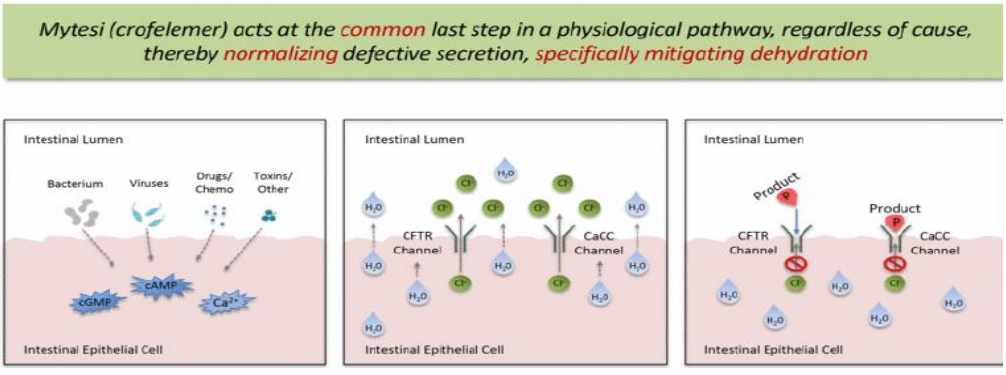
Crofelemer Has a Novel Mechanism of Action

Crofelemer has a novel mechanism of action on two chloride channels in the intestine. These channels, the cystic fibrosis transmembrane conductance regulator (CFTR) and the calcium-activated chloride channel anoctamin 1, regulate the flow of chloride ions. Crofelemer blocks these channels to prevent outflow of chloride and water from the cells and the diarrhea, ion imbalance, and dehydration that results.

Crofelemer's size and polarity prevent it from being absorbed systemically, limiting its action to the intestinal lumen. These is no effect on gastric motility or other ion channels in the intestine that would affect electrolytes or fluids. These factors give a low incidence of adverse events and no known clinically significant interactions with other drugs. The CFTR receptor function in the colon is conserved across mammalian species, making its use in animals predictive of human indications.

Crofelemer's highly specific mechanism of action has potential for use in many forms of secretory diarrhea, a form caused by disturbance of the normal cellular activity of the cells in the intestine. This is typically caused by drugs, hormones, bacterial toxins and poisons, or diseases. Jaguar has tested crofelemer in a variety of indications that have provided supporting data of its efficacy.

Exhibit 3: Crofelemer's Mechanism of Action in the Intestine



Source: Jaguar Health, Inc.

Crofelemer Is Marketed as Mytesi for HIV/AIDS Antiviral-Related Diarrhea

Mytesi (crofelemer) was approved for symptomatic relief of noninfectious diarrhea in adults with HIV/AIDS on antiretroviral therapy. The approval was based on the data from the ADVENT trial, showing efficacy and safety.

The Phase 3 ADVENT clinical trial enrolled 376 HIV-positive patients on anti-retroviral therapy. Patients received a dose of 125 mg twice daily or placebo. The results showed significantly reduced secretory diarrhea in the treated patients assessed over a 4-week period. The trial had a 5-month placebo-free extension phase and a 48-week, open-label safety study. There were no serious adverse events, and no appreciable effect on immune parameters, such as HIV viral load and CD4+ cell counts. The overall incidence of adverse events was similar in the crofelemer and placebo groups.

In July 2017, a poster presentation at the 9th IAS Conference on HIV Science updated the clinical effects of Mytesti. "Long Term Crofelemer Provides Clinically Relevant Reductions in HIV-Related Diarrhea" (MacArthur RD; Clay P, Glick G, et al.) showed outcomes from patients treated with Mytesi twice a day for 20 weeks. The data showed that 89% (151 out of 162) patients treated had a decrease in diarrhea. Of those, 83% had a 50% decrease, 72% had a 75% decrease, and 56% had a 100% decrease (no watery stools). We believe these data provide additional support for Mytesi's efficacy.

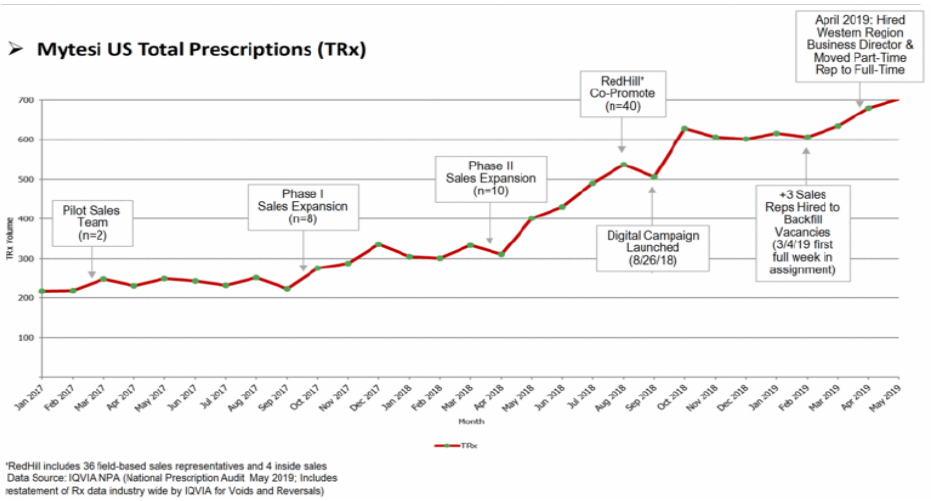
Jaguar's Marketing Program Has Improved Sales

After receiving product approval in 2012, the product was named Fulyzaq and introduced by Salix Pharmaceuticals. It did not receive the marketing support needed and never achieved significant market penetration. Upon regaining the product rights in 2016, it was renamed Mytesi and relaunched with a new marketing campaign.

Although total prescriptions, patients on drug, and sales have improved, Jaguar is directing resources to other indications. The company found that the HIV/AIDS community is focused on prevention and getting new patients on anti-retroviral therapy. Since the source of diarrhea can be attributable to many factors, doctors give greater attention to managing other side effects and keeping patients on therapy. Over-the-counter drugs like Immodium or Kaopectate remain common for short-term use. Jaguar has adapted its marketing and support, and we expect modest sales growth in this indication.

Importantly, the patient use has produced a large safety database including chronic, long-term use. This safety and dosing schedule have been the basis for additional trials in other indications. The safety database has been accepted by the FDA for Phase 3 trials in chemotherapy and for the supplemental application for label expansion.

Exhibit 4: Mytesi Prescription Trends Have Improved



Source: Jaguar Health, Inc.

Label Expansion in Other Conditions

Chemotherapy Treatment-Related Diarrhea Can Be a Dose Limiting Side Effect: Side effects of chemotherapy can be so difficult to tolerate that patients stop therapy to let their bodies recover. Introduction of drugs to control anemia, neutropenia, and chemotherapy-induced nausea and vomiting have allowed treatments to continue on schedule, improving patient outcomes and survival. However, one side-effect that still has no effective treatment is diarrhea.

Some of the most effective cancer drugs in clinical use act by blocking cell surface receptors or intracellular signals. Monoclonal antibody drugs directed against surface receptors (EGFR, HER2, VEGF, PGDF) block the receptor activation that signals tumor growth and proliferation. Protein kinase inhibitors act inside the cell to stop pathways that lead to cell survival, growth, and proliferation. While monoclonal antibodies and protein kinase inhibitors are highly effective, they are also associated with diarrhea. Some combination regimens can have such high incidence and severity of diarrhea that patients stop treatment or doctors will not use them at all.

The lead indication of crofelemer is for cancer treatment-related diarrhea (CTD). The first trial testing crofelemer with chemotherapy regimens is the HALT-D study. This is an investigator-initiated trial at Georgetown University evaluating crofelemer prophylaxis with HER2-positive breast cancer chemotherapy regimen.

The HALT-D study has enrolled patients with breast cancer treated with the combination of Herceptin (trastuzumab) and Perjeta (pertuzumab), with either Taxotere (docetaxel) or Taxol (paclitaxel) (THP), or the combination of or trastuzumab, pertuzumab, docetaxel, and carboplatin (TCHP). The patients are randomized to two treatment arms receiving 125mg crofelemer twice daily or placebo. Trastuzumab and pertuzumab and are both monoclonal antibodies from Genentech used to treat HER-2 positive breast cancer. The study was initiated and sponsored by Genentech with support from Jaguar.

Studies testing these combination regimens have shown high efficacy but have an incidence of up to 72% for all grades of diarrhea and up to 12% for Grade 3 diarrhea. This grade of diarrhea can hospitalize the patient due to dehydration, hypotension, and can lead to renal failure. The risk of severe CTD is enough for doctors to avoid using the drug combination.

An interim analysis of about 23 patients is expected to be announced in 3Q19, with the full study enrollment of 51 patients expected in 1Q20. This is expected to be a futility analysis to determine if there is a "positive interim result" sufficient to continue the study, defined the result as a difference of 20% or greater.

The primary endpoint is incidence of all grade diarrhea for more than 2 consecutive days during cycles 1 to 2 of THP or TCHP. We expect the full study results to include incidence and severity of diarrhea, as well as time to first diarrheal episode, frequency, duration, stool quality over time, and use of alternative anti-diarrhea medications. These endpoints are intended to determine if crofelemer can make the chemotherapy regimens more tolerable and improve quality of life.

Phase 3 Design Is in Progress

In March 2019, the company met with the FDA to discuss the design of a Phase 3 trial in CTD. The agency determined that the existing safety database was acceptable for the application, and no additional non-clinical studies are needed. The Chemistry Manufacturing and Control data are also sufficient, and no new drug interaction studies are needed.

The Phase 3 pivotal trial design is expected to have a 12-week treatment period in which crofelemer is administered concomitantly with targeted cancer therapies. The primary endpoint will be the proportion of responders achieving a pre-specified number of weekly water bowel movements over the study period and/or the number proportion of diarrhea-free days (number of patient-days having zero watery bowel movements) over the 12-week period. Enrollment criteria and statistical analysis are not yet finalized, although enrollment is expected to be in the range of 250 to 275 patients for 80% power.

We believe this trial design would support the label expansion for relief of diarrhea in patients receiving targeted chemotherapies with or without cycle chemotherapy. As shown in Exhibit 5, this could include many chemotherapy regimens that lead to diarrhea. The current cost of $22 per day for Mytesi is at the low end of the range for antiemetic drugs for chemotherapy and vomiting (CINV), which we believe would be acceptable to third-party payers.

Severe Diarrhea Has Prevented Neratinib Use

Nerlynx (neratinib) is a tyrosine kinase inhibitor developed by Puma Biotechnology (PBIY, $11.89, Not Rated). The tyrosine kinase inhibitor category works through a mechanism that mediates calcium dependent chloride transport, and is associated with high rates of diarrhea.

Neratinib was approved in 2017 for the treatment of patients with early stage HER2-overexpressed/amplified breast cancer after trastuzumab based therapy. The data showed that one year of neratinib following trastuzumab improved two-year invasive disease–free survival rate compared with placebo.

The Phase 3 ExteNET clinical trial enrolled patients with early-stage HER2-positive breast cancer who had undergone surgery and adjuvant treatment with trastuzumab. After completing trastuzumab, patients received extended treatment with either neratinib or placebo for a period of one year. Two years later, invasive disease-free survival (iDFS) was 94.2% in the treatment group compared with 91.9% in the placebo group (Hazard ration 0.66; 95% CI: 0.49, 0.90, p=008). However, the rate of diarrhea was 95% in the treated patients, with 39.9% of the patients reaching Grade 3. In studies where patients were treated prophylactically with loperamide, the incidence of Grade 3 diarrhea was still 17%.

Although it was shown to be beneficial and received FDA approval, the high rate of diarrhea has limited its use. Initial sales estimates were in the multibillion-dollar range, yet 2018 sales reached only $200 million.

An investigator at UCSF designed a clinical study to test crofelemer prophylaxis for preventing diarrhea from neratinib treatment. The trial was designed to follow the regimen in the product label, enrolling patients who have undergone surgery and completed adjuvant treatment with trastuzumab, followed by neratinib for one year. Crofelemer prophylaxis would be given during the first two cycles of treatment than as needed for the remaining months of the study.

However, this study has not treated any patients. The investigator found the risk of diarrhea too high and has not moved forward with the study. We see this as an example of how crofelemer could enable use of an effective drug that improves patient outcomes.

Few Effective Treatments for Chemotherapy Treatment-Related Diarrhea

The drugs given to CID patients are common anti-diarrheals intended for short-term use. These are either anti-motility drugs that act by slowing the passage of material through the intestine, absorbents that increase the amount of water removed from the material, or anti-secretory drugs that reduce water flow into the intestine.

The commonly used drug for CTD is loperamide (Immodium), a synthetic opioid that acts as mu_2-opioid receptor agonist in the intestines. It decreases smooth muscle tone in the intestinal wall, slowing the passage of material through the intestine. This increases time for water to be absorbed and reduces diarrhea. Tincture of Opium (Laudanum) is a stronger opioid that is about 10% powdered opium, comparable to 1% morphine. Tincture of Opium also acts on the mu_2-opioid receptor to slow peristalsis but is a highly controlled substance and must be dosed carefully to avoid constipation or ileus.

Another drug sometimes used with CTD is octreotide, a somatostatin analogue. Octreotide decreases hormone secretion to increase time for material to pass through the intestinal, increase electrolyte absorption, and decrease mesenteric blood flow. However, octreotide also has effects on insulin, glucagon, and growth hormone and is reserved for persistent diarrhea that does not respond to loperamide.

Pepto-Bismol is a common over-the-counter drug used for mild stomach upset and diarrhea. It is a salicylic acid derivative that reduces inflammation and hypermotility of the stomach, with anti-bacterial action to eliminate the causes of stomach problems. In addition, its anti-secretory action stimulates absorption of fluids and electrolytes, reducing diarrhea. It is not a strong anti-diarrheal, and its use for chronic diarrhea is limited.

Additional Indications Include Potential Orphan-Drug Indications

Crofelemer's non-secretory mechanism of action has potential for use in many conditions where non-infectious diarrhea can be a serious problem. Jaguar has data from clinical trials in several conditions in which crofelemer has been tested, including indications for infants and children with congenital diarrheal disorders (CDDs) and short bowel syndrome (SBS). Safety studies have been completed for pediatric applications to treat children as young as three months of age. Orphan-drug designation has been received for pediatric short bowel syndrome.

Congenital Diarrheal Disorders (CDDs) are a group of genetic digestive diseases with a typical onset from birth to the first years of life. Although many CDDs have variable outcomes, severe chronic diarrhea is the main clinical symptom. Lack of sufficient intestinal absorptive function can cause dehydration, malnutrition, metabolic acidosis, and failure to thrive. Therapy must be started immediately to prevent dehydration and long-term complications, including long-term disabilities or death.

CDDs are related to specific genetic defects inherited as autosomal recessive traits, with highest incidence in regions where consanguineous marriage is common. One affected group is the royal family in the United Arab Emirates. Jaguar Health was contacted by a doctor at the Sheikh Khalifa Medical City in Abu Dhabi, a 586-bed medical center managed by the Cleveland Clinic, who requested information about crofelemer. These discussions led to an investigator-initiated trial of crofelemer for CDD in children. Jaguar is planning to submit an IND to begin trials with a feeding tube formulation of crofelemer in 2H19.

Short Bowel Syndrome is a rare digestive disorder in which the patient lacks sufficient small intestinal length to absorb nutrients properly. This is often caused by surgical removal the small intestine to control Crohn's disease, damage from necrotizing enterocolitis, or congenital deficiencies in the small intestine. The predominant symptom is diarrhea, causing dehydration, weight loss, and complications from malnutrition.

Traveler's Diarrhea, one of the common causes of acute diarrhea, is a stomach and intestinal infection caused by bacteria while traveling, commonly known as traveler's diarrhea. This commonly affects travelers in the first two weeks, causing diarrhea and may also have cramps and nausea. Most travelers recover within four days, but about 10% will have symptoms lasting a week or more.

A Phase 2 study was conducted to evaluate the effectiveness of crofelemer in the treatment of traveler's diarrhea. The study tested three doses of crofelemer, enrolling 184 patients from the United States who had traveled to Jamaica or Mexico. Subjects were

randomized into double-blind, placebo-controlled groups then treated with 125 mg, 250 mg, or 500 mg crofelemer or a matching placebo four times a day for 2 days.

The mean time interval from taking the first dose of medication until passage of the last unformed stool during 48-hour therapy (TLUS48) was 38.7 hours for the placebo group compared with 30.6 h for the 125-mg dose group (p = 0.005), 30.3 h for the 250-mg group, and 32.6 h for the 500-mg group (p = 0.01). Crofelemer was well tolerated at all doses.

We view the data supportive of the mechanism of action and efficacy but do not see traveler's diarrhea as a separate indication. We have not included any revenues in our models.

Clinical Testing for Lechlemer Is Planned for Cholera

Lechlemer is a second-generation derivative made from the sap from the *Croton lechleri* tree. It has the same mechanism of action as crofelemer, is also sustainably harvested, and is much less expensive to produce. Lechlemer is a distinct product from crofelemer, with a lead indication in cholera and general watery diarrhea.

Cholera is an acute, diarrheal illness caused by infection in the intestine by the bacterium *Vibrio cholerae*. This is a common illness in certain geographies, with an estimated worldwide incidence of 3-5 million cases and over 120,000 deaths each year. The infection is often mild or without symptoms, although approximately 5-10% of those infected will progress to severe disease. Symptoms include profuse watery diarrhea, vomiting, electrolyte imbalance, and cramps. The rapid loss of body fluids leads to dehydration and shock. Without treatment, death can occur within hours.

Jaguar has conducted small Phase 2 studies treating cholera with crofelemer. In our opinion, data from these studies demonstrates efficacy of the drug and supports its mechanism of action. These results are being used to design a new trial using lechlemer.

In June 2019, the company announced that the National Institute of Allergy and Infectious Diseases (NIAID, part of the National Institutes of Health) will provide preclinical support services for lechlemer development. NIAID-funded contractors will conduct toxicology testing for 7-day rat and dog studies. We see this action as a positive development that is both a recognition of the drug's potential and a financial benefit for Jaguar.

As a new compound for cholera, lechlemer would qualify for a Priority Review Voucher (PRV) under the Section 524 of the Food Drug Act Amendments Act of 2007. This legislation authorized the FDA to grant priority review vouchers as an incentive to develop treatments for small neglected tropical diseases, rare pediatric diseases, and medical countermeasures.

PRVs are submitted with an NDA to shorten the review time from the standard 10 months to 6 months, allowing the new drug to reach the market sooner. PRVs can be sold to other companies who can use them to accelerate reviews of drugs that have high sales potential. Over the past two years, PRVs have sold for between $80 to $150 million, with $105 million as the most recent sale in March 2019.

Animal Health: Although animal health is no longer the focus of the company, crofelemer's mechanism of action is highly conserved in mammalian species. Jaguar plans to continue work in animals where it can provide data for human development or continue previous work that can lead to sales without large investments.

Jaguar is planning to complete the application for approval for Canalevia, the canine formulation of crofelemer. The application is submitted in sections, with the last of four sections planned for filing with the FDA's Center for Veterinary Medicine during 3Q19. The company expects to receive conditional approval for chemotherapy induced diarrhea (CID) in dogs that will allow for launch in veterinary markets during 1H20.

We see this as a legacy product that Jaguar can market with limited additional investment. Since the mechanism of action is conserved between dogs and humans, it allows the company to gather efficacy and dose limitation feedback from veterinarians who can use Canalevia with less restrictions than human doctors.

We have not included revenues from this indication in our models at this time. An estimated 230,000 dogs in the US undergo chemotherapy each year, with diarrhea as a common side effect. Veterinarians dispense medications as part of their practice and make significant mark-ups, giving them incentive to use them. Dog owners having their pets treated for cancer are likely to add a drug that can reduce diarrhea and accidents in their homes.

Financial Models and Valuation

Our financial models are based expectations of positive interim results from the HALT-D study and successful results in 2020. We anticipate Phase 3 beginning in late 2020 and running to about mid-2021. Allowing for submission of an application for label expansion in early 2022, we expect approval and launch of the chemotherapy indication around late 2022, with first revenues in 2023. We have not included earlier sales, although Mytesi is an approved product and could be used off-label.

Our earnings estimates are based on use of crofelemer in targeted chemotherapy regimens, similar to the HALT-D study and the anticipated product label. The number of new cancer diagnoses in the US is estimated at 14 million each year. Of these, about 4 million receive chemotherapy. The number of breast cancer patients in the US is estimated at 1.1 million, with about 260,000 new cases each year. Our models are based on the breast cancer indication beginning in 2023, with increasing use in other cancers following.

We model crofelemer in newly diagnosed breast cancer patients with 65,000 patients treated each quarter. We assume patients treated with targeted chemotherapies use crofelemer for an average of three quarters during the first year of therapy. Assuming patients start therapy at an even rate throughout the quarter, we model an average of 1.0 months (66% compliance) usage per patient per quarter. This would be below the clinical trial regimen of every day for a year.

We expect moderate use in other targeted chemotherapy regimens for other cancer types. Based on 1 million patients treated per quarter, we assume patients use the drug for only the first month after treatment. Our revenues are based on the number of patients taking crofelemer in a single quarter, with no continuation from previous quarters.

Our models assume sales growth in the HIV/AIDS indication about 10% in the coming year. There are an estimated 1.1 million people in the US alone with HIV, and an estimated 20% get diarrhea from their anti-retroviral medications. This estimate could increase if news from the chemotherapy trial data raises awareness of the drug.

We have not included revenues from other indications that are expected to start Phase 2 trials in the coming year. Congenital Diarrhea Disease, Short Bowel Syndrome, and Idiopathic Diarrhea could all bring potential increases to our models. Lechlemer, the second-generation drug, could also be a breakthrough for cholera. We have not included any valuation for lechlemer or a priority review voucher.

The company recently completed an offering to provide $16.6 million in capital. The offering included common and preferred convertible stock, with two series of warrants exercisable at $2.00 per share. Our estimates for shares outstanding assume all warrants are exercised by mid-2020.

We value the company based on our 2024 EPS of $1.03, discounted at 30% per year. Applying a multiple of 15X, we derive a price target of $5 per share.

Risk Factors

Risks to our rating and price target include but are not limited to:

Drug development risk: Jaguar Health is a development stage company conducting clinical trials for its lead product. The company faces the risks of the drug development industry, including scientific, technical, clinical, regulatory failures. As novel therapies, the drugs also face risks with reimbursement and product adoption.

Company risks: The company has a limited operating history, expects to incur further losses as it grows and maybe unable to achieve or sustain profitability. Its independent registered public accounting firm has expressed doubt about their ability to continue as a going concern. The company's principal stockholders own a significant percentage of voting stock and will be able to exert significant control over matters subject to stockholder approval.

Emerging growth company: The company is considered an emerging growth company and due to the reduced operating requirements applicable to emerging growth companies, certain investors may find investing in their securities less attractive.

International risks: The international aspects of their business expose the company to business, regulatory, political, operational, financial and economic risks associated with doing business outside of the US. Certain of the countries in which the company plans to commercialize its products in the future are developing countries, some of which have potentially unstable political and economic climates. Fluctuation in the exchange rate of foreign currencies could result in currency transaction losses.

Intellectual property risk: The field of patents and intellectual property involves complex scientific and legal issues that are subject to change by legislation or judicial action. Other companies with greater resources may challenge the company through the legal system or in the marketplace. Changes in US patent law could diminish the value of patents in general, thereby impairing the company's ability to protect its products.

Clinical supplies and manufacturing risk: Jaguar Health leases its operating facilities and relies on third party suppliers for its clinical trial grade materials, including the active pharmaceutical ingredients. We believe the supply of clinical materials is sufficient to conduct the trials, but third party manufacturing still carries a risk of problems or disagreements that could cause delays.

Regulatory risk: The company has conducted several clinical trials, and although we believe the pre-clinical and early clinical data indicate efficacy, further testing is needed before market approval. The findings from clinical trials must be reviewed by the FDA before the company receives approval to continue clinical testing. Analysis by the FDA may not agree with the analysis presented by the company. Approval of licensing applications cannot be assumed.

Exchange and market risk: JAGX shares trade on the NASDAQ exchange with relatively small daily volume. The company is expected to raise additional capital to fund operations before its products reach the market, which is subject to market conditions. The company has a previous purchase agreement with Oasis capital. The sale of common stock to Oasis Capital may cause substantial dilution to existing shareholders and the sale of the shares of common stock acquired by Oasis Capital could cause the price of the common stock to decline.

Legislation and policy changes: Laws for drug approval are established by Congress and administered by the FDA. Reimbursement by third-party payors often follows policies established by the Center for Medicaid/Medicare. Both agencies are divisions of the Department of Health and Human Services, run by Commissioners appointed by the President and confirmed by the Senate. Changes in policies or political agendas could have broad effects on the environment for drug development and reimbursement.

Jaguar Animal Health: Income Statement ($000)															
JAGX: Year Ending December 31	**2018A**	**1Q19A**	**2Q19A**	**3Q19E**	**4Q19E**	**2019E**	**1Q20E**	**2Q20E**	**3Q20E**	**4Q20E**	**2020E**	**2021E**	**2022E**	**2023E**	**2024E**
Product sales															
Collaborative revenue	177														
Animal Health															
Mytesi - HIV/AIDS	4,239	1,590	1,706	1,825	1,925	7,045	1,800	1,950	2,100	2,200	8,050	8,800	9,600	10,560	11,616
Mytesi - Breast Cancer														42,998	78,146
Mytesi - All Cancers														35,000	35,000
Total Sales	**4,416**	**1,590**	**1,706**	**1,825**	**1,925**	**7,045**	**1,800**	**1,950**	**2,100**	**2,200**	**8,050**	**8,800**	**9,600**	**77,998**	**113,146**
Total Product Sales	**4,416**	**1,590**	**1,706**	**1,825**	**1,925**	**7,045**	**1,800**	**1,950**	**2,100**	**2,200**	**8,050**	**8,800**	**9,600**	**77,998**	**113,146**
Expenses															
Cost of products sold	2,766	865	1,260	1,186	1,251	4,563	1,170	1,268	1,365	1,430	5,233	5,280	4,800	16,878	16,972
%COGS	*63%*	*54%*	*74%*	*65%*	*65%*	*65%*	*65%*	*65%*	*65%*	*65%*	*65%*	*60%*	*50%*	*22%*	*15%*
Research and development	5,155	1,421	1,698	1,900	2,100	7,119	2,400	2,300	2,500	2,800	10,000	11,200	13,600	14,000	17,000
Sales and marketing expense	9,832	1,565	2,173	2,300	2,500	8,538	2,750	2,750	3,000	3,000	11,500	13,000	14,500	16,000	17,500
General and Administrative	12,277	3,513	3,197	3,250	3,400	13,360	3,250	3,250	3,500	3,500	13,500	16,000	17,000	17,500	19,000
Impairment of goodwill	5,211														
Impairment of indefinite-lived assets			4,000												
Total expenses	**35,240**	**7,365**	**12,329**	**8,636**	**9,251**	**33,580**	**6,820**	**6,818**	**7,365**	**7,730**	**28,733**	**32,480**	**35,400**	**48,378**	**52,972**
Operating Income (Loss)	(30,824)	(5,775)	(10,623)	(6,811)	(7,326)	(26,535)	(5,020)	(4,868)	(5,265)	(5,530)	(20,683)	(23,680)	(25,800)	29,620	60,174
Interest expense	(2,629)	(547)	(3,657)	(1,500)	(500)	(6,204)	(500)	(500)	(500)	(500)	(2,000)	(2,000)	(8,000)	(8,000)	(8,000)
Other income	316	6	14	10	9	40	10	10	10	10	40	40	40	40	40
Change in fair value of warrants	331	(46)	207	(100)	(100)	(39)	(100)	(100)	(100)	(100)	(400)	(400)	(400)	(400)	(400)
Gain on Valeant settlement	1,204														
Loss on extinguishment of debt	(544)	(1,942)	(2,663)												
Total other income	**(1,322)**	**(2,529)**	**(6,099)**	**(1,590)**	**(591)**	**(6,203)**	**(590)**	**(590)**	**(590)**	**(590)**	**(2,360)**	**(2,360)**	**(8,360)**	**(8,360)**	**(8,360)**
Pretax Income	**(32,146)**	**(8,304)**	**(16,722)**	**(8,401)**	**(7,917)**	**(32,738)**	**(5,610)**	**(5,458)**	**(5,855)**	**(6,120)**	**(23,043)**	**(26,040)**	**(34,160)**	**21,260**	**51,814**
Accretion of redeemable converible preferred stock															
Income Tax Provision (Benefit)												(2,604)	(6,832)	5,315	15,544
Tax Rate												*10%*	*20%*	*25%*	*30%*
GAAP Net Income (loss)	**(32,146)**	**(8,304)**	**(16,722)**	**(8,401)**	**(7,917)**	**(32,738)**	**(5,610)**	**(5,458)**	**(5,855)**	**(6,120)**	**(23,043)**	**(23,436)**	**(27,328)**	**15,945**	**36,270**
GAAP-EPS (basic)	**(197.82)**	**(9.78)**	**(15.11)**	**(0.81)**	**(0.76)**	**(5.76)**	**(0.54)**	**(0.16)**	**(0.17)**	**(0.18)**	**(0.81)**	**(0.67)**	**(0.78)**	**0.45**	**1.03**
GAAP EPS (diluted)	(197.82)	(9.78)	(15.11)	(0.81)	(0.76)	(5.76)	(0.54)	(0.16)	(0.17)	(0.18)	(0.81)	(0.67)	(0.78)	0.45	1.03
Weighted Average Shares (basic, in thousands)	163	849	1,106	10,381	10,391	5,682	10,402	34,622	34,656	34,691	28,593	34,778	34,917	35,057	35,197
Weighted Average Shares (diluted, in thousands)	163	849	1,106	10,381	10,391	5,682	10,402	34,622	34,656	34,691	28,593	34,778	34,917	35,057	35,197

Source: Company reports and Ladenburg Thalmann

Jaguar Animal Health, Inc: Balance Sheet											
Assets	**2018E**	**1Q19A**	**2Q19A**	**3Q19E**	**4Q19E**	**2019E**	**2020E**	**2021E**	**2022E**	**2023E**	**2024E**
Cash and Cash Equivilents	$2,568	$2,572	$1,606	$10,132	$2,635	$2,635	$42,984	$33,923	$9,178	$27,808	$66,864
Restricted cash											
Accounts receivable	996	915	2,097	2,097	2,097	2,097	2,097	2,097	2,097	2,097	2,097
Other receivable	6	2	93	93	93	93	93	93	93	93	93
Due from related party											
Inventory	3,342	2,960	2,393	2,393	2,393	2,393	2,393	2,393	2,393	2,393	2,393
Deferred offering costs			336	336	336	336	336	336	336	336	336
Prepaid expenses	1,238	866	823	823	823	823	823	823	823	823	823
Deferred finance charges											
Other current assets											
Total current assets	$8,150	$7,315	$7,348	$15,873	$8,377	$8,377	$47,903	$38,842	$14,097	$32,727	$71,783
Property and equipment, net	761	745	737	737	737	737	737	737	737	737	737
Restricted cash											
Deferred finance charges											
Goodwill											
Intangible assets, net	31,711	31,289	26,867	26,867	26,867	26,867	21,693	21,693	21,693	21,693	21,693
Operating lease right-of-use-asset		1,078	906	906	906	906	906	906	906	906	906
Other assets	421	235	208	208	208	208	208	208	208	208	208
Total assets	$41,042	$40,663	$36,066	$44,592	$37,096	$37,096	$71,448	$62,386	$37,642	$56,271	$95,328
Liabilities:											
Accounts payable	5,414	6,564	6,390	6,390	6,390	6,390	6,390	6,390	6,390	6,390	6,390
Deferred collaborative revenue											
Convertible notes payable	11,239	11,150									
Notes payable	4,846	1,259	3,563	3,563	3,563	3,563	3,563	3,563	3,563	3,563	3,563
Warrant liability	220	1,275	5,182	5,182	5,182	5,182	5,182	5,182	5,182	5,182	5,182
Accrued expenses	4,939	3,981	5,274	5,274	5,274	5,274	5,274	5,274	5,274	5,274	5,274
Long-term debt - current portion											
Derivative liability											
Conversion option liability											
Operating lease liability		522	426	426	426	426	426	426	426	426	426
Deferred rent											
Total current liabilities	$26,659	$24,750	$20,835	$20,835	$20,835	$20,835	$20,835	$20,835	$20,835	$20,835	$20,835
Convertible debt, net of discount											
Notes payable, net of discount			7,760	7,760	7,760	7,760	7,760	7,760	7,760	7,760	7,760
Deferred rent											
Deferred tax liability											
Operating lease liability		116	116	116	116	116	116	116	116	116	116
Total liabilities	$26,659	$24,867	$28,711	$28,711	$28,711	$28,711	$28,711	$28,711	$28,711	$28,711	$28,711
Stockholders' equity											
Series A redeemable preferred stock	9,000	9,000	9,000	9,000	9,000	9,000	9,000	9,000	9,000	9,000	9,000
Series B convertible preferred stock				10,787	10,787	10,787	-	-	-	-	-
Common stock	2	6	0	2	2	2	5	5	5	5	5
Common stock, non-voting	4	4	4	4	4	4	4	4	4	4	4
Additional paid-in capital	99,927	109,641	117,928	124,066	124,487	124,487	184,255	198,629	201,213	203,898	206,684
Accumulated deficit	(94,551)	(102,855)	(119,577)	(127,978)	(135,895)	(135,895)	(153,328)	(176,764)	(204,092)	(188,147)	(151,877)
Total stockholders equity	5,383	6,796	(1,645)	(3,906)	(11,403)	(11,403)	30,937	21,875	(2,869)	15,760	54,817
Total Liab & Equity	$41,042	$40,663	$36,066	$44,592	$37,095	$37,095	$68,648	$59,586	$34,842	$53,471	$92,528
Shares Issued (in thousands)	163	849	1,106	10,381	10,391	5,682	28,593	34,778	34,917	35,057	35,197
Shares Outstanding (in thousands)	163	849	1,106	10,381	10,391	5,682	28,593	34,778	34,917	35,057	35,197

Source: Company reports and Ladenburg Thalmann

Jaguar Animal Health: Cash Flow Statement ($000)											
Cash flows from operating activities:	**2018A**	**1Q19A**	**2Q19A**	**3Q19E**	**4Q19E**	**2019E**	**2020E**	**2021E**	**2022E**	**2023E**	**2024E**
Net income (loss)	(32,146)	(8,304)	(25,026)	(33,427)	(41,344)	(41,344)	(23,043)	(23,436)	(27,328)	15,945	36,270
Stock-based compensation	2,024	427	873	1,200	1,600	1,600	1,750	1,900	2,200	2,300	2,400
Depreciation and amortization	1,319	437	873	873	873	873	823				
Loss on extinguishment of debt	544	1,942	4,605	4,605	4,605	4,605					
Amortization of debt issuance costs and debt discount	1,197	178	3,879	3,879	3,879	3,879					
Change in fair value of warrants	(6)	46	(161)	(161)	(161)	(161)					
Impairment of goodwill	5,211										
Impairment of indefinite-lived intangilble assets			4,000	4,000	4,000	4,000					
Interest paid on converstion of debt to equity	21										
Common stock issued in exchange for services	6										
Warrants issued for services	24										
Amortization of operating lease right-of-use assets		57	363	363	363	363					
Changes in assets and liabilities:											
Accounts receivable	(528)	81	(1,102)	(1,102)	(1,102)	(1,102)					
Other receivable	(5)	4	(87)	(87)	(87)	(87)					
Inventory	(1,269)	382	949	949	949	949					
Prepaid expenses and other current assets	(112)	150	248	248	248	248					
Other long-term assets	(263)	27									
Deferred revenue	(177)										
Deferred rent	109										
Accounts payable	(1,941)	1,150	976	976	976	976					
Accrued expenses	3,260	52	1,067	1,067	1,067	1,067					
Operating lease liabilities		(93)	(230)	(230)	(230)	(230)					
Net Cash Used in Operating Activities	**(22,731)**	**(3,466)**	**(8,772)**	**(16,846)**	**(24,363)**	**(24,363)**	**(17,669)**	**(21,536)**	**(25,128)**	**18,245**	**38,670**
Cash flows from investing activities:											
Purchase of equipment	(7)		(7)	(7)	(7)	(7)					
Cash paid in Napo merger, net of cash acquired											
Net cash provided by investing activities	**(7)**	**0**	**(7)**	**(7)**	**(7)**	**(7)**	**0**	**0**	**0**	**0**	**0**
Cash flows from financing activities:											
Repayment of notes payable		(100)	(100)	(100)	(100)	(100)					
Repayment of long-term debt	(1,689)										
Proceeds of issuance of redeemable convertible notes payable, net	474										
Proceeds from issuance of common stock	7,056	2,769	2,869	8,682	8,703	8,703	58,018	12,475	383	385	386
Proceeds from issuance of Series B convertible preferred stock				10,787	10,787	10,787					
Proceeds from issuance of convertible preferred stock (Series A)	9,199										
Proceeds from issuance of common stock July 2018	625										
Proceeds from issuance of common stock October 2018	6,945										
Payments of underwriting discounts, commissions, and offering costs	(2,118)		(3)	(3)	(3)	(3)					
Issuance of common stock - exercise of prepaid equity forward contracts	2,055										
Fractional common shares repurchased	(0)										
Proceeds from issuance of notes payable			5,050	5,050	5,050	5,050					
Payments of long-term debt											
Net cash provided by financing activities	24,546	3,469	7,816	24,416	24,437	24,437	58,018	12,475	383	385	386
Effect of exchange rate on cash and cash equivalents											
Net Increase (decrease) in cash and cash equivilents	1,808	4	(962)	7,564	67	67	40,349	(9,061)	(24,745)	18,630	39,056
Cash and equivalents, beginning of period	760	2,568	2,568	2,568	2,568	2,635	42,984	33,923	9,178	27,808	66,864
Cash and equivalents, end of period	2,568	2,572	1,606	10,132	2,635	2,635	42,984	33,923	9,178	27,808	66,864

Source: Company reports and Ladenburg Thalmann

APPENDIX A: IMPORTANT RESEARCH DISCLOSURES

ANALYST CERTIFICATION

I, Robert M. LeBoyer, attest that the views expressed in this research report accurately reflect my personal views about the subject security and issuer. Furthermore, no part of my compensation was, is, or will be directly or indirectly related to the specific recommendation or views expressed in this research report, provided, however, that:

The research analyst primarily responsible for the preparation of this research report has or will receive compensation based upon various factors, including the volume of trading at the firm in the subject security, as well as the firm's total revenues, a portion of which is generated by investment banking activities.

Additional information regarding the contents of this publication will be furnished upon request. Please contact Ladenburg Thalmann, Compliance Department, 277 Park Avenue, 26th floor, New York, New York 10172 (or call 212-409-2000) for any information regarding current disclosures, and where applicable, relevant price charts, in regard to companies that are the subject of this research report.

COMPANY BACKGROUND

Jaguar Health, Inc., is a commercial stage pharmaceuticals company, focusing on developing gastrointestinal products for human prescription use and animals worldwide. The company, through its wholly-owned subsidiary, Napo Pharmaceuticals, Inc., focuses on developing and commercializing proprietary human gastrointestinal pharmaceuticals for the global marketplace from plants used traditionally in rainforest areas. Its human health product pipelines include crofelemer, which is in Phase 2 clinical trial for the treatment of cancer therapy-related diarrhea. Additional trials are for supportive care in inflammatory bowel disease, short bowel syndrome, congenital diarrheal disorders, idiopathic/functional diarrhea, and irritable bowel syndrome. A second-generation anti-secretory agent is in development for multiple indications, including cholera. The company's animal health product candidates comprise Canalevia, an animal prescription drug product candidate intended for treatment of chemotherapy-induced diarrhea in dogs; and Equilevia, a non-prescription product for total gut health in equine athletes. In addition, the company's products include Neonorm Calf and Neonorm Foal.

VALUATION METHODOLOGY

We value JAGX based on our 2024 EPS estimate of $1.03, discounted at 30% with a multiple of 15X. Our price target is $5 per share.

RISKS

Risks to our rating and price target include but are not limited to:

Drug development risk: Jaguar Health is a development stage company conducting clinical trials for its lead product. The company faces the risks of the drug development industry, including scientific, technical, clinical, regulatory failures. As novel therapies, the drugs also face risks with reimbursement and product adoption.

Company risks: The company has incurred significant losses and negative cash flow operations since inception and they expect to incur losses and negative cash flows for at least the next 12 months. Their independent registered public accounting firm has expressed doubt about their ability to continue as a going concern.

Emerging growth company: The company is considered an emerging growth company and due to the reduced operating requirements applicable to emerging growth companies, certain investors may find investing in their securities less attractive.

International risks: The international aspects of their business expose the company to business, regulatory, political, operational, financial and economic risks associated with doing business outside of the US.

Intellectual property risk: The field of patents and intellectual property involves complex scientific and legal issues that are subject to change by legislation or judicial action. Other companies with greater resources may challenge the company through the legal system or in the marketplace.

Clinical supplies and manufacturing risk: Jaguar Health leases its operating facilities and relies on third party suppliers for its clinical trial grade materials, including the active pharmaceutical ingredients. We believe the supply of clinical materials is sufficient to conduct the trials, but third party manufacturing still carries a risk of problems or disagreements that could cause delays.

Regulatory risk: The company has conducted several clinical trials, and although we believe the pre-clinical and early clinical data indicate efficacy, further testing is needed before market approval. The findings from clinical trials must be reviewed by the FDA before the company receives approval to continue clinical testing. Analysis by the FDA may not agree with the analysis presented by the company. Approval of licensing applications cannot be assumed.

Exchange and market risk: JAGX shares trade on the NASDAQ exchange with relatively small daily volume. The company is expected to raise additional capital to fund operations before its products reach the market, which is subject to market conditions.

Legislation and policy changes: Laws for drug approval are established by Congress and administered by the FDA. Reimbursement by third-party payors often follows policies established by the Center for Medicaid/Medicare. Both agencies are divisions of the Department of Health and Human Services, run by Commissioners appointed by the President and confirmed by the Senate. Changes in policies or political agendas could have broad effects on the environment for drug development and reimbursement.

STOCK RATING DEFINITIONS

Buy: The stock's return is expected to exceed 12.5% over the next twelve months.

Neutral: The stock's return is expected to be plus or minus 12.5% over the next twelve months.

Sell: The stock's return is expected to be negative 12.5% or more over the next twelve months.

Investment Ratings are determined by the ranges described above at the time of initiation of coverage, a change in risk, or a change in target price. At other times, the expected returns may fall outside of these ranges because of price movement and/or volatility. Such interim deviations from specified ranges will be permitted but will become subject to review.

RATINGS DISPERSION AND BANKING RELATIONSHIPS AS OF (September 12, 2019)

Rating	%	IB %
BUY	73.6	56.8
NEUTRAL	26.4	34.0
SELL	0.0	0.0

COMPANIES UNDER ROBERT'S COVERAGE

Jaguar Health, Inc. (JAGX)
Outlook Therapeutics, Inc. (OTLK)
Oramed Pharmaceuticals, Inc. (ORMP)

COMPANY SPECIFIC DISCLOSURES

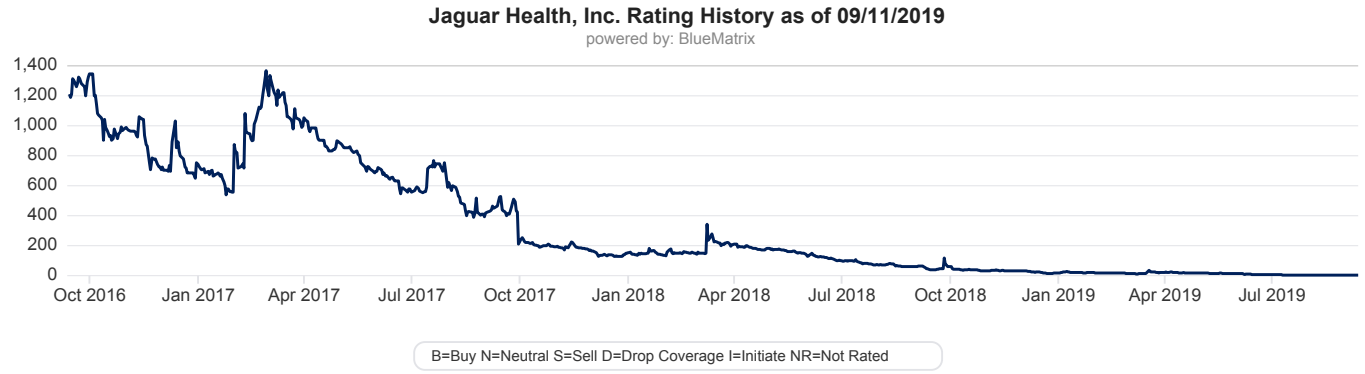
Ladenburg Thalmann & Co. Inc. makes a market in Jaguar Health, Inc..

Ladenburg Thalmann & Co. Inc. has managed or co-managed a public offering for Jaguar Health, Inc. within the past 12 months.

Ladenburg Thalmann & Co. Inc received compensation for investment banking services from Jaguar Health, Inc. within the past 12 months.

Ladenburg Thalmann & Co. Inc had an investment banking relationship with Jaguar Health, Inc. within the last 12 months.

INVESTMENT RATING AND PRICE TARGET HISTORY



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