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SCHEDULE 14A

Proxy Statement Pursuant to Section 14(a) of
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Check the appropriate box:

o Preliminary Proxy Statement

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JAGUAR HEALTH, INC.

(Name of Registrant as Specified In Its Charter)

(Name of Person(s) Filing Proxy Statement, if other than the Registrant)

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June 25, 2020

DEAR FELLOW MEMBERS OF JAGUAR AND NAPO'S GLOBAL FAMILY:

I was recently reading the adult noir fiction novel *Bottle Grove* by David Handler. As anyone who has children is likely aware, Daniel Handler is also known as Lemony Snicket, author of the great young adult *A Series of Unfortunate Events* stories. The series of thirteen novels comprising *A Series of Unfortunate Events* tell the story of three siblings who become orphans when an unfortunate event happens to their parents.

Lemony Snicket's stories struck me.

In a very real sense, Mytesi®, our precious drug product, has been orphaned. A product granted approval for noninfectious diarrhea in adults with HIV/AIDS on antiretroviral therapy (ART)—our goal when we put Mytesi in clinical trials more than 15 years ago for the hundreds of thousands of people living with HIV (PLWH) and associated unrelenting diarrhea—is now orphaned. What does that mean? Yes, Mytesi is the only oral plant-based, non-opioid, fair trade-sourced medicine approved by the FDA under botanical guidance. Yes, our team fought and prevailed in a six-year legal battle to regain control of this first-in-class drug we developed which was allegedly being neglected by a commercial partner that had other potentially competitive plans in place.

And now, here we are in 2020, recognizing that less than 5,000 PLWH are currently being prescribed Mytesi.

Mytesi has been orphaned.

Is that an unfortunate event? Is that not a success? What is success for an emerging drug discovery pharmaceutical company?

I personally know several PLWH who are on Mytesi. Their lives are transformed. They get out of the house. They hold down a job. They have (better) sex. They escape isolation and humiliation. They adhere to their life-saving ART meds.

As many of you know, our team has been collaborating since 1990 with local and Indigenous peoples in Peru who are part of the flow of resources supporting the supply of crofelemer, Mytesi's active ingredient. We estimate that 4,000 people are involved in the sustainable harvest, reforestation, transport, documentation and export of the sap of the *Croton lechleri* tree from which crofelemer is extracted and purified – a number that is not much smaller than the number of people currently being prescribed Mytesi. This symmetry of interdependence – whereby both patients in the U.S. and people in the rainforest are benefiting from Mytesi – is another important part of this story. We have remained in partnership with these people in Peru, their families, and their communities throughout our many years of developing Mytesi and we will continue to do so. We personally know many of the local and Indigenous people who continue to plant *Croton lechleri* trees in their nearby forests, and who in turn continue to receive important income for the daily needs of their families. We proudly consider these people, families, and communities to be an integral part of our shared Mytesi success story.

If our efforts have an important impact on even a small number of people, and harm no one, are we successful?

I say yes. We say yes. We say that is why we went into this business.

It is a business, though, and we of course have more to do.

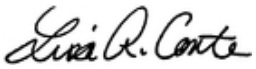
We did not know Mytesi would be orphaned, yet here we are. We embrace the neglected comorbidity of diarrhea in our PLWH population, and hug them tight with newly enhanced patient access programs under the umbrella of NapoCares. This is working. We move a product derived and purified from a rainforest tree that has been utilized for centuries as part of traditional medicine by the local and Indigenous peoples who taught us about its medicinal properties, to the shelf of essentially any U.S. pharmacy, and remove barriers to those in need.

What more? We believe there are many patient populations around the world that can potentially benefit from Mytesi: For instance, people with cancer therapy-related diarrhea; people with IBS; people who need supportive care for IBD and Crohn's; and children who suffer from rare pediatric diseases such as congenital diarrheal disease and short bowel syndrome could benefit from the symptomatic relief provided by Mytesi.

Our mission, our vision, our survival are intertwined goals tied to expanding the benefits, the reach, and (to be technical) the "labelled indications" we extend to such populations.

Together with our employees, our families, our many loyal and dedicated investors, and the local and Indigenous communities with which we partner, we are a family. Yes, we've been orphaned, but only for the time being. We embrace our pathways to new, broader, bigger complementary populations, informed by the wisdom and experience gained bringing our precious Mytesi from the rainforest to the market, and encouraging the participation of new partners to bring Mytesi to all those in need.

Sincerely,



Lisa A. Conte
Chief Executive Officer & President

Overview of Pipeline Products

Company Overview

Jaguar Health is a commercial stage pharmaceutical company focused on developing and commercializing novel drug products for treating gastrointestinal diseases on a global basis. Crofelemer, the active ingredient in Mytesi®, is a plant-based drug extracted and purified from the red bark sap of the *Croton lechleri* tree found in the Amazon Rainforest. Crofelemer is a non-opiate antidiarrheal drug indicated for the symptomatic relief of noninfectious diarrhea in adult patients with HIV/AIDS on antiretroviral therapy, Mytesi is marketed by Jaguar's wholly owned subsidiary Napo Pharmaceuticals, Inc. ("Napo") and is the only plant-based oral medicine approved by the FDA under botanical guidance. There are currently no other FDA-approved anti-secretory products, which act locally in the gut and have an excellent tolerability and safety profile for long term use like crofelemer. Crofelemer represents a new drug in the management of gastrointestinal disease symptoms.

We believe Jaguar is poised to realize a number of synergistic, value adding benefits—and an expanded pipeline of potential human follow-on indications of crofelemer, along with a second-generation anti-secretory drug candidate—upon which to build global partnerships. Jaguar, through Napo, holds extensive global rights for Mytesi, and crofelemer manufacturing is being conducted at a multimillion-dollar commercial manufacturing facility that has been FDA-inspected and approved. Additionally, several of the drug product candidates in Jaguar's Mytesi pipeline are backed by strong Phase 2 (i.e. clinical) proof of concept evidence from completed human trials, and we are pursuing business development partnerships to progress pipeline development globally.

Napo recently expanded the NapoCares™ patient support program for Mytesi. A key component of the enhanced NapoCares program involves offering significantly expanded support for eligible patients to reduce out of pocket costs as a barrier to obtaining Mytesi in the U.S. The income limit to the patient assistance program, which offers free drug for uninsured patients, has increased from two-times the federal poverty limit to five-times the federal poverty limit, an 150% increase, and the Mytesi copay benefit for commercially insured patients has been increased from an annual maximum of $1,200 to $6,000, which is a 400% increase. The enhancements also allow the copay amount to remain the same whether a patient fills a 30-day or 90-day prescription of Mytesi. Most eligible patients will now pay as little as $25 for their Mytesi prescription. These changes became effective April 1, 2020.

Our new market access strategy is designed to significantly increase the number of specialty pharmacies involved in Mytesi distribution. Specialty pharmacies offer a high touch patient engagement model to help ensure appropriate use of drugs like Mytesi and optimal patient outcomes.

We are removing barriers for patients to access Mytesi, and this sustainable commercial business effort supports our strategy to become a stable, cash flow positive business supported primarily by growth in sales of Mytesi for its approved indication.

Product Development Overview

PRODUCT	INDICATION	DEVELOPMENT STAGE				
		PRECLINICAL	PHASE 1	PHASE 2	PHASE 3	MARKET
Mytesi	Noninfectious diarrhea in adults with HIV/AIDS antiretroviral therapy					
Mytesi	Cancer therapy-related diarrhea (CTD)					
Mytesi	Supportive care for IBD					
Formulation of crofelemer	Rare Disease Short Bowel Syndrome (SBS) & Congenital Diarrheal Disease (CDD)			*Orphan-drug status previously received for SBS; applying for orphan-drug status for CDD*		
Mytesi	IBS - Diarrhea Predominant (IBS-D)				*Paper published*	
Mytesi	Idiopathic/functional diarrhea			*Study initiated and sponsored by the University of Texas Health Science Center at Houston*		
Lechlemer*	Cholera and other GI indications (second generation anti-secretory agent)		*Received preclinical services funded by the National Institute of Allergy and Infectious Diseases for dog and rat toxicity studies*			

*Potential opportunity for Priority Review Voucher (PRV)

Cancer Therapy-related Diarrhea

Crofelemer is in late-stage development for the intended indication of symptomatic relief of cancer therapy-related diarrhea (CTD). A significant proportion of patients undergoing targeted cancer therapy with or without standard chemotherapy experience diarrhea. Novel targeted cancer therapy agents, such as epidermal growth factor receptor (EGFRs) antibodies and tyrosine kinase inhibitors (TKIs), with or without cycle chemotherapy agents, may activate intestinal chloride channel pathways leading to increased chloride secretion into the gut lumen, coupled with significant loss of water that would result in secretory diarrhea.

Market Size/Potential: An estimated 650,000 U.S. cancer patients receive chemotherapy in an outpatient oncology clinic. Comparable supportive care (i.e., CINV) product sales of ~$620 million in 2013. Global CINV market projected to reach a valuation of $2.7 billion by 2022 (Report published by Allied Market Research, titled, "Chemotherapy-induced Nausea and Vomiting (CINV) Market-Global Opportunity Analysis and Industry Forecast, 2014-2022" (https://www.prnewswire.com/news-releases/chemotherapy-induced-nausea-and-vomiting-cinv-market-expected-to-reach-2659-million-by-2022-611755395.html)

Napo met with the FDA in 2019 to discuss the planned protocol for Napo's Phase 3 clinical trial in cancer subjects to evaluate the effects of Mytesi in providing symptomatic relief of CTD. That meeting, which included academic key opinion leaders and/or Napo Scientific Advisory Board members from leading oncology treatment institutions, resulted in a productive regulatory discussion about clinical trial design and endpoint requirements for the CTD pivotal trial.

Competition: We are not aware of any FDA-approved drugs specifically indicated for CTD. A recent Phase 2b trial of elsiglutide for the treatment of chemotherapy induced diarrhea in colorectal cancer patients did not meet statistical significance. Opioids and over the counter drugs are commonly used to treat chemotherapy induced diarrhea, but these drugs affect gut motility and produce constipation. Certain tyrosine-kinase inhibitor targeted therapy agents have diarrhea as a significant side effect. For example,

FDA guidance suggests prophylaxis with loperamide prior to initiating adjuvant therapy with neratinib, a pan-HER tyrosine kinase inhibitor for HER2-positive breast cancer.

Key Agreements from the FDA Interactions:

- Agreement for a single pivotal trial to support approval for the proposed follow-on indication in CTD
- Agreement for no additional nonclinical safety studies, (Mytesi is already approved for chronic use)
- Agreement for no additional manufacturing requirements, since Mytesi is already commercially manufactured under GMP and is commercialized in the US
- Agreement for no additional drug-drug interaction studies, based on crofelemer's locally acting mechanism of action and lack of any significant effects on metabolism

Ongoing Investigator-Initiated Trial (IIT) Utilizing Mytesi to Evaluate Effects in Breast Cancer Patients: Enrollment is ongoing for the HALT-D study in breast cancer patients receiving regimens containing Herceptin and Perjeta. Study Objective: *HALT-D: DiarrHeA Prevention and ProphyLaxis with Crofelemer in HER2 Positive Breast Cancer Patients Receiving Trastuzumab, Pertuzumab, and Docetaxel or Paclitaxel with or without Carboplatin*. The study is expected to be completed in late-2020. The study is being conducted at Georgetown University and funded by Genentech, a member of the Roche Group.

Preclinical Study Evaluating Effects of Crofelemer for Symptomatic Relief of Diarrhea in Dogs Receiving Neratinib: Napo has announced the results from a preclinical pharmacological study that evaluated the effects of crofelemer on diarrhea induced in healthy dogs receiving neratinib, a pan-HER tyrosine kinase inhibitor (TKI).

- Results show crofelemer reduced the incidence and severity of diarrhea in dogs, and also showed a trend for enabling maintenance of a higher dose (approximately 20%) of the neratinib
- Dogs receiving crofelemer twice daily or four times daily with neratinib had significantly lower number of watery stools per week and improved stool consistency from unformed to formed stools over the 28-day study period
- These results have been presented at the recently concluded American Association of Cancer Research (AACR) meeting
- These precilinical results also provide key scientific rationale to support the use of crofelemer in providing symptomatic relief of noninfectious diarrhea in human patients receiving TKI-and/or-other targeted cancer therapy-containing regimens in the planned pivotal trial

Next Steps: The company expects to file the Investigational New Drug (IND) application for crofelemer for CTD in mid-2020, and to initiate the pivotal trial for CTD in 2H 2020.

Other Relevant Studies: While Jaguar's commercial and development efforts have evolved to focus primarily on Mytesi and human pipeline indications since its merger with Napo, we are continuing limited initiatives related to Canalevia™, our drug product candidate for treatment of chemotherapy-induced diarrhea (CID) in dogs. We believe dog experience, such as the above preclinical study with neratinib in dogs, is predictive of the expected benefit of crofelemer in human patients suffering from cancer therapy-related diarrhea. With receipt of conditional approval for CID, the company expects the product to be commercially available for this indication in dogs in Q2 2021. We also expect Canalevia to be available for treatment of exercise-induced diarrhea (EID) in dogs in Q2 2021.

Supportive Care Potential for Crofelemer to Address Diarrhea from Inflammatory Bowel Disease

Inflammatory bowel disease (IBD) is a term for two conditions (Crohn's disease and ulcerative colitis) that are characterized by chronic inflammation of the gastrointestinal (GI) tract where patients often have persistent diarrhea. Key opinion leaders ("KOLs") identified an unmet need to treat diarrhea in IBD patients, particularly in specific subsets of patients such as the IBD patients who undergo ileal pouch-anal anastomosis (IPAA) surgery who experience severe, chronic diarrhea following the procedure. Because this is a highly-motivated patient population with a low placebo-responder risk, we believe a relatively small proof-of-concept trial is the appropriate next step from a development standpoint. KOLs felt

crofelemer's novel mechanism of action might also prove to be an effective treatment for diarrhea that results from bile acid malabsorption, which has been shown to occur in approximately 30% of patients with IBD.

Additionally, gastroenterology KOLs felt crofelemer's novel mechanism of action might prove to be an effective treatment for diarrhea experienced by patients receiving IV infusions of Entyvio®, a Takeda Pharmaceuticals prescription medicine used in adults with moderate to severe ulcerative colitis or Crohn's disease.

Market Size/Potential: An estimated 1,171,000 Americans have IBD (Source: Kappelman, M. et al. Recent Trends in the Prevalence of Crohn's Disease and Ulcerative Colitis in a Commercially Insured US Population. Dig Dis Sci. 2013 Feb; 58(2): 519-525).

Clinical Study: Mytesi has demonstrated good tolerability and safety in clinical studies that support chronic use for multiple supportive care indications, including in IBD patients. The next steps would include conducting a Phase 2 proof of concept study for supportive care in patients with IBD.

Planned Clinical Trial in Pediatric Patients with Congenital Diarrheal Disorders

A novel liquid formulation of crofelemer is in development to provide symptomatic relief of diarrhea in orphan-drug indications for infants and children with congenital diarrheal disorders (CDDs).

CDDs are a group of rare, chronic intestinal channel disorders, with onset in early infancy, that are characterized by severe, lifelong diarrhea and a lifelong need for nutritional intake either parenterally or with a feeding tube. CDDs are related to specific genetic defects inherited as autosomal recessive traits. The incidence of CDDs is prevalent in regions where consanguineous marriage (related by blood) is part of the culture. CDDs are directly associated with serious secondary conditions including dehydration, metabolic acidosis, and failure to thrive, prompting the need for enteral and parenteral nutritional support to prevent death and limit life-long disability.

We have previously received orphan-drug status for Mytesi from the FDA Office of Orphan Products Development (OOPD) for the potential short bowel syndrome (SBS) adult and pediatric patients. The mission of the OOPD is to advance the evaluation and development of products (drugs, biologics, devices, or medical foods) that demonstrate promise for the diagnosis and/or treatment of rare diseases or conditions with an occurance of less than 200,000 patients.

Market Size/Potential: CDD and SBS are true rare disease indications. We are still sizing the markets globally, though both diseases are more prevalent in cultures where consanguineous marriage is more common.

Competition: We are not aware of any FDA-approved drugs specifically indicated for symptomatic relief of diarrhea associated with Congenital Diarrheal Disorders and/or Short Bowel Syndrome.

Clinical Studies: We have previously completed safety studies of crofelemer in children as young as three months of age with respiratory syncytial virus (RSV) infections. A Phase 2 safety and tolerability study in infants and children, aged between 3 months and 17 years is being planned to be conducted following the completion of development of a pediatric formulation and authorization for initiation of a pediatric clinical trial. The study would be conducted at premier US institutions and ex-US institutions such as Sheikh Khalifa Medical City (SKMC) in Abu Dhabi. Additionally, rationale from some pre-clinical at investigations in CDD patient intestinal cells will be conducted to support the CDD clinical study.

Next Steps: The company has received feedback from the FDA following its pre-IND submission in Q1 2020 on the key requirements for the pediatric CDD study. The company expects to file the Investigational New Drug (IND) application for crofelemer for CDD in Q4 2020.

Irritable Bowel Syndrome—Diarrhea Predominant (IBS-D)

Irritable bowel syndrome (IBS) is a gastrointestinal condition defined by abdominal pain and altered bowel habits in the absence of another disease that can account for these symptoms. Diarrhea is a common symptom in a subset of IBS, a frustrating, underdiagnosed and undertreated condition. IBS-D is a subtype characterized mainly by loose or watery stools at least 25 percent of the time. Patients with IBS, but particularly those with IBS-D, report significantly reduced quality of life, higher indirect costs, and greater impairments in daily and work activities.

Abdominal pain is the key symptom of IBS, and the pain, which is associated with a change in stool frequency or consistency, can be severe. To improve the diagnosis and outcomes for IBS patients and to update clinicians on the latest research, Dr. William Chey, a gastroenterologist and professor of medicine and nutrition sciences at the University of Michigan, along with an international team of collaborators, compiled Rome IV, an updated compendium of diagnostic criteria on functional GI disorders such IBS. Rome IV contains a chapter titled Centrally Mediated Disorders of Gastrointestinal Pain.

Although new agents for IBS-D have been FDA approved and are marketed by various manufacturers, there is an unmet medical need for long-term, safe management of the abdominal pain associated with IBS-D. We recognize that patients suffering from IBS-D may require a poly-pharmacy approach to lifetime management of their disease. Mytesi, which represents a novel mechanistic approach with the benefit of a long-term safety profile, could possibly be an important addition to the treatment of IBS-D, if approved for this indication. Napo published the results from a phase 2 clinical trial in women with IBS-D in December 2019 that showed improvement in abdominal pain and discomfort in subjects receiving crofelemer when compared to those receiving matching placebo in a 3 month multicenter clinical trial.

Market Size/Potential: Most IBS products have an estimated revenue potential of greater than $1.0 billion (Source: Merrill Lynch forecasts peak US sales of roughly $1.5 bn for Ironwood's Linzess (https://247wallst.com/healthcare-business/2015/04/27/key-analyst-sees-nearly-30-upside-in-ironwood/); Rodman & Renshaw estimate peak annual sales of Synergy Pharmaceuticals' Trulance at $2.3 bn in 2021 (https://www.benzinga.com/analyst-ratings/analyst-color/17/04/9304883/what-synergys-new-patents-mean-for-its-commercial-prospe). According to the U.S. FDA, studies estimate that IBS affects 10 to 15 percent of adults in the United States. IBS is more prevalent in women than in men.

Competition: Two drugs were approved in 2015 for the treatment of diarrhea predominant irritable bowel syndrome, Allergan plc's Viberzi® and Salix Pharmaceuticals' Xifaxan®, which is marketed by Valeant Pharmaceuticals International. Also, Sebela Pharmaceuticals' Lotronex® was approved by the FDA in 2000 but was withdrawn from the market and later reintroduced in 2002 under a Risk Management Program. We are seeking a partner to further the clinical development and commercialization of crofelemer for d-IBS. There are currently numerous trials ongoing for d-IBS.

If we receive regulatory approval for Mytesi for IBS, we expect to compete with major pharmaceutical and biotechnology companies that operate in the gastrointestinal space, such as Sucampo AG, Takeda Pharmaceuticals, Allergan, Inc., Ironwood Pharmaceuticals, Synergy Pharmaceuticals, Sebela Pharmaceuticals, and Salix Pharmaceuticals. Because Mytesi is approved for a chronic indication and several of the other agents have safety concerns, there is likely to be an opportunity for a polypharmaceutical approach to long-term management of these patients, removing a direct competitive scenario from Mytesi's potential entry to the marketplace and disease indication.

Clinical Studies: Mytesi has been demonstrated to be safe for chronic use, and two studies provide statistically significant results of crofelemer use for abdominal pain in women.

Phase 2—a randomized double-blind placebo-controlled, dose-ranging (placebo, 125 mg, 250 mg, and 500 mg bid) study over a 12-week treatment period in 246 patients with d-IBS (Rome II criteria), including both males and females, whose average age was 50 years old: A study appearing in the December 2019 issue of Clinical and Translational Gastroenterology, a peer-reviewed journal published by the American College of Gastroenterology, indicates that crofelemer could be a treatment option for abdominal pain associated with diarrhea-predominant irritable bowel syndrome (IBS-D). This multicenter, phase 2, randomized, double-blind, placebo-controlled trial evaluated the effect of crofelemer on abdominal pain in women with IBS-D. A total of 240 women were enrolled, and participants were randomized to crofelemer (125 mg) or placebo twice daily for 12 weeks. Following an analysis by the FDA-issued revised recommendations for outcome measures in IBS clinical trials in 2010, the proportion of monthly abdominal pain responders was significantly higher in the crofelemer group during months 1 through 2 (58.3% vs 45.0%, p = 0.030) as well as during the entire 3 months (54.2% vs 42.5%, p = 0.037) when compared with placebo. No significant differences were observed in the proportion of stool consistency monthly responders based on the revised FDA guidelines.

Idiopathic/Functional Diarrhea

Chronic idiopathic diarrhea is a common complaint of patients presenting to family practitioners and internists, and is one of the most common reasons for referral to gastroenterologists.

Market Size/Potential: It is estimated that the prevalence of chronic idiopathic diarrhea in developed countries (including the U.S.) is approximately 3-5%. The American Gastroenterological Association Burden of Illness study (2012) showed that the estimated annual direct and indirect costs associated with chronic idiopathic diarrhea is up to $524 million per year and $136 million per year, respectively.

Clinical Studies: A clinical research study initiated and sponsored by The University of Texas Health Science Center at Houston (UTHealth) is being supported by Napo. The study will evaluate the safety and effectiveness of crofelemer for treatment of chronic idiopathic diarrhea in patients, which has a significant negative effect on health-related quality of life and causes a high economic burden on patients and society. The principal investigator for the Study is Dr. Brooks D. Cash, MD, AGAF, FACG, FACP, FASGE, Chief - Division of Gastroenterology, Hepatology and Nutrition, Sterling Professor of Medicine, McGovern Medical School at UTHealth, Co-Director, Ertan Digestive Disease Center at Memorial Hermann-Texas Medical Center. The study is titled Yield of Diagnostic Tests and Management of Crofelemer for Chronic Idiopathic Diarrhea in Non-HIV Patients: A Pilot Study, and is a single-center trial at UTHealth.

Crofelemer is also being evaluated in another investigator-initiated trial for the management of functional diarrhea in non-HIV patients. The principal investigator for this planned clinical study is Dr. Anthony Lembo, Professor, Gastroenterology, Beth Israel Deaconess Medical Center, Harvard Medical School. This clinical study is a randomized double-blind, placebo-controlled study in adult subjects with functional diarrhea. Eligible patients will have functional diarrhea defined by Rome IV criteria as >25% loose watery stools and <25% hard/lumpy stools. The study plans to randomize 80 patients and the subjects will be randomized 1:1 for 4 weeks to either the placebo or crofelemer 125 mg delayed-release tablets (Mytesi) arm, administered twice daily for 4 weeks. Following the four-week placebo-controlled period, all subjects will receive Mytesi for an additional four weeks in an open label extension phase. The safety and tolerability of crofelemer and the clinical response during the placebo-controlled period will be evaluated in this study. Subjects will be allowed to use limited amounts of an antimotility drug (loperamide) during the placebo-controlled and open-label extension phase to manage uncontrolled diarrhea. However, no more than 11 doses of 2 mg loperamide will be permitted during any given week per subject. This study is planned to be initiated in the second half of 2020 and is estimated to be completed in the second half of 2021.

Cholera/General Watery Diarrhea

We are investigating lechlemer for the indication of cholera/general watery diarrhea in adults and children. According to the Centers for Disease Control and Prevention of the U.S. Department of Health & Human Services, cholera is an acute, diarrheal illness caused by infection of the intestine with the bacterium *Vibrio cholerae*. The infection is often mild or without symptoms but can sometimes be severe. Approximately one in 10 (5-10%) of infected persons will have severe disease characterized by profuse watery diarrhea, vomiting, and leg cramps. In these people, rapid loss of body fluids leads to dehydration and shock. Without treatment, death can occur within hours. At this time, for example, the largest cholera outbreak in recorded history is occurring in Yemen.

Lechlemer is a distinct and proprietary Napo pharmaceutical formulation of a standardized botanical extract, also sustainably derived from the *Croton lechleri* tree. We believe lechlemer represents a long-term pipeline opportunity as a second-generation anti-secretory agent, on a global basis, for multiple gastrointestinal diseases. Additionally, we believe lechlemer, which has the same mechanism of action as crofelemer and is significantly less costly to produce, may support efforts to receive a priority review voucher from the U.S. FDA for a cholera indication. Priority review vouchers are granted by the FDA to drug developers as an incentive to develop treatments for neglected diseases and rare pediatric diseases. If approved for this indication, lechlemer could serve as long-term pipeline anti-secretory agent for cholera/general watery diarrhea in geographies where cost of goods is a critical factor, for example, in resource-constrained regions and countries in which a requirement exists for drug prices to decrease annually.

Market Size/Potential: An estimated 3-5 million cases and over 100,000 deaths occur each year around the world. In recent transactions by other companies, priority review vouchers have sold for $67 million to $350 million. (Source: In Aug. 2015, AbbVie Inc. bought a priority review voucher from United Therapeutics Corp for $350 million (https://www.wsj.com/articles/united-therapeutics-sells-priority-review-voucher-to-abbvie-for-350-million-1439981104). In July 2014, BioMarin announced that it had sold a priority review voucher to Sanofi and Regeneron for $67.5 million. (Source: https://investors.biomarin.com/2014-07-30-BioMarin-Sells-Priority-Review-Voucher-for-67-5-Million).

Competition: We are not aware of any FDA-approved drugs specifically indicated as an anti-secretory agent for use to address the devastating dehydration in cholera patients.

Clinical Studies: We have previously conducted multiple animal and human studies in acute diarrheal conditions with lechlemer. We have prior experience in cholera patients with crofelemer, which has the same anti-secretory mechanism of action, as lechlemer, thus providing us with clinical and scientific rationale for this indication.

Two preclinical toxicology studies in rats and dogs have been completed with lechlemer to support the continued development of lechlemer for the symptomatic relief of diarrhea from cholera and potentially other acute infectious diarrheal conditions. Completion of these initial studies allows the initiation of longer-term toxicity and safety pharmacology studies, including 28-day toxicity studies in rats and dogs, that the company expects will support the Investigational New Drug (IND) application the company plans to file for lechlemer. As previously announced, Napo received preclinical services supported by the National Institute of Allergy and Infectious Diseases ("NIAID") to support development of lechlemer. NIAID is part of the National Institutes of Health. Under NIAID's suite of preclinical services, NIAID-funded contractors conducted the initial 7-day rat and dog toxicology studies. As mentioned above, Napo has previously conducted a study in adult cholera patients as well as other non-cholera related acute diarrheal conditions with crofelemer, which provide the requisite rationale for the mechanism of action (MOA) of lechlemer as well as guidance for future clinical studies.

Phase 2 study of crofelemer in the treatment acute, severely dehydrating watery diarrhea with confirmed cholera with the use of an antibiotic (azithromycin) and oral rehydration therapy in 100 adult patients between 18 and 55 in Bangladesh: A total of 100 adult patients, from Bangladesh, between the ages of 18 and 55, with acute, severely dehydrating watery diarrhea with confirmed cholera were treated with

crofelemer on a background of an antibiotic (azithromycin) and oral rehydration therapy. After a four-hour period of rapid rehydration therapy, patients were randomized 1:2:2 to placebo or 125 mg or 250 mg oral dose of crofelemer. Crofelemer or placebo doses were administered about one hour after the oral administration of azithromycin (1 gm dose). The primary objective was to evaluate the safety and effects of crofelemer on reducing the watery stool output normalized to body weight (mL/kg) in the first 24 hours on the background of azithromycin and rehydration therapy. Crofelemer was well tolerated and there were no drug related adverse events in this study. Both doses of crofelemer produced approximately 25-30% reduction in median watery stool volumes in the 0-6 and 0-12 hour period following initiation of therapy. Crofelemer showed a strong trend in the reduction of watery stool output in the 0-6 hour and 0-12 hour intervals (p=0.07). Upon exclusion of three outlier patients, the crofelemer dose of 125 mg produced a statistically significant reduction in the normalized stool output (p=0.028), and the dose of 250 mg crofelemer showed a strong trend for reduction of watery stool output (p=0.07).

In another study, the effects of crofelemer were evaluated in patients with acute dehydrating watery diarrhea caused by various bacterial pathogens, such as enterotoxic strains of *Escherichia coli* (ETEC) and Vibrio cholerae infection. Crofelemer was evaluated in adult Indian patients with acute watery diarrhea of less than 24-hour duration with suspected bacterial infections, without the use of antibiotics. In this study, patients received oral doses of placebo or crofelemer at a dose of 250 mg every 6 hours for 2 days on the background of oral rehydration therapy only. The use of antibiotics was prohibited in this study. A total of 98 patients were randomized into this study (47 in placebo group and 51 in the crofelemer group). Primary endpoints for this study were changes in stool weight, frequency, consistency, duration of diarrhea. Secondary endpoints included the assessment of clinical symptoms scored as a total of 7-item GI index. Clinical success was defined as no diarrhea within 48 hours from the study start date, and treatment failure was defined as no improvement/worsening of symptoms after 24 hours, fever, bloody stools or dehydration.

Results: 98 patients (51 crofelemer, 47 placebo) were enrolled in the study. Sixteen patients (4 in the crofelemer group and 12 in the placebo group) used antibiotics and were considered as treatment failures and were excluded from the "per protocol efficacy analysis." Groups were similar in age, weight, vital signs, stool frequency, consistency, dehydration and GI index.

The crofelemer group had improvement over baseline and compared to placebo at day 3. More specifically, crofelemer showed superior effects in reducing stool weight (61% vs 11%), stool frequency (65% vs 21%), reversion to soft stool (92% vs 49%) and improved the 7-item GI index (70% C vs 33% P), (all $p<0.05$). Crofelemer was well tolerated with no related serious adverse events or concerning changes in lab values. Progression to dehydration and report of fecal incontinence was more common in the placebo group ($p<0.05$).

Conclusions: Clinical success (cessation of diarrhea within 48 hours of 1st dose) was achieved in 79% of crofelemer patients compared to 28% placebo patients ($p<0.05$).

Next Steps: The company expects to file the Investigational New Drug (IND) application for lechlemer for cholera in 1H 2021 (subject to funding).

About Mytesi®

Mytesi (crofelemer) is an antidiarrheal indicated for the symptomatic relief of noninfectious diarrhea in adult patients with HIV/AIDS on antiretroviral therapy (ART). Mytesi is not indicated for the treatment of infectious diarrhea. Rule out infectious etiologies of diarrhea before starting Mytesi. If infectious etiologies are not considered, there is a risk that patients with infectious etiologies will not receive the appropriate therapy and their disease may worsen. In clinical studies, the most common adverse reactions occurring at a rate greater than placebo were upper respiratory tract infection (5.7%), bronchitis (3.9%), cough (3.5%), flatulence (3.1%), and increased bilirubin (3.1%).

See full Prescribing Information at Mytesi.com. Crofelemer, the active ingredient in Mytesi, is a botanical (plant-based) drug extracted and purified from the red bark sap of the medicinal *Croton lechleri* tree in the

Amazon rainforest. Napo has established a sustainable harvesting program for crofelemer to ensure a high degree of quality and ecological integrity.

Forward-Looking Statements

Certain statements in this document constitute "forward-looking statements." These include statements regarding the belief that Jaguar is poised to realize a number of synergistic, value adding benefits—and an expanded pipeline of potential human follow-on indications of crofelemer, along with a second-generation anti-secretory agent—upon which to build global partnerships, the expectation that the company will finalize the agreement for the single pivotal CTD trial with the FDA, the expectation regarding the timing of the availability of the completion timing of the HALT-D study, the belief that dog experience, such as the TKI study in dogs, is predictive of the expected benefit of crofelemer in human patients suffering from CTD, the expectation that, with receipt of conditional approval of Canalevia for CID and EID, the product will be commercially available for these indications in dogs in 2021, the belief that believe lechlemer represents a long-term pipeline opportunity as a second-generation anti-secretory agent, on a global basis, for multiple gastrointestinal diseases, the expectation that lechlemer may support efforts to receive a PRV from the U.S. FDA for a cholera indication, the expectation that lechlemer, if approved for the cholera indication, could serve as long-term pipeline anti-secretory agent for cholera/general watery diarrhea in geographies where cost of goods is a critical factor, for example, in resource-constrained regions and countries in which a requirement exists for drug prices to decrease annually, and statements regarding the timing of other planned studies and IND filings. In some cases, you can identify forward-looking statements by terms such as "may," "will," "should," "expect," "plan," "aim," "anticipate," "could," "intend," "target," "project," "contemplate," "believe," "estimate," "predict," "potential" or "continue" or the negative of these terms or other similar expressions. The forward-looking statements in this document are only predictions. Jaguar has based these forward-looking statements largely on its current expectations and projections about future events. These forward-looking statements speak only as of the date of this document and are subject to a number of risks, uncertainties and assumptions, some of which cannot be predicted or quantified and some of which are beyond Jaguar's control. Except as required by applicable law, Jaguar does not plan to publicly update or revise any forward-looking statements contained herein, whether as a result of any new information, future events, changed circumstances or otherwise. Neither this document nor its delivery to any person should constitute or form part of a prospectus or an offer to sell or a solicitation of an offer to buy any security or offer to enter into any other transaction or commercial agreement, or a commitment of any nature on the part of Jaguar.