# Preclinical Study Demonstrating Symptomatic Relief of Diarrhea in Dogs Receiving Neratinib in Combination with Crofelemer (Mytesi) Presented at American Association for Cancer Research Virtual Annual Meeting

June 23, 2020

***Conducted by Jaguar Health subsidiary Napo Pharmaceuticals in collaboration with Puma Biotechnology, the study provides scientific rationale for the use of crofelemer in treating cancer patients receiving targeted therapy agents such as tyrosine kinase inhibitors***

**SAN FRANCISCO, CA / ACCESSWIRE / June 23, 2020 /** Jaguar Health, Inc. (NASDAQ:JAGX) ("Jaguar" or the "Company") announced today that a preclinical study evaluating the effects of crofelemer (Mytesi®) in providing symptomatic relief of diarrhea associated with the irreversible pan-HER tyrosine kinase inhibitor (TKI) neratinib (Nerlynx®) is being presented as an e-poster at the American Association for Cancer Research Virtual Annual Meeting II, which takes place June 22 - 24, 2020. The study was conducted by Jaguar subsidiary Napo Pharmaceuticals, Inc. ("Napo") in collaboration with Puma Biotechnology, Inc.

Mytesi, a novel non-opiate chloride ion channel modulator antidiarrheal drug, is currently indicated for the symptomatic relief of noninfectious diarrhea in adult patients with HIV/AIDS on antiretroviral therapy. Nerlynx, a drug product of Puma Biotechnology, Inc., is a pan HER TKI indicated for the extended adjuvant treatment of adult patients with early stage HER2 positive breast cancer and also for metastatic HER2 positive breast cancer.

This study provides scientific rationale for the use of crofelemer in providing symptomatic relief of watery diarrhea in patients receiving a targeted cancer therapy drug like neratinib with or without cycle chemotherapy in future clinical studies.

"This 28-day preclinical pharmacological study in healthy female dogs was designed to evaluate the scientific rationale for the use of crofelemer in reducing the severity and incidence of diarrhea associated with a tyrosine kinase inhibitor (neratinib)," said Dr. Michael Guy, DVM, Ph.D., Jaguar's vice president of preclinical and nonclinical studies. "The study was conducted without the prophylaxis or concomitant use of loperamide and demonstrated that crofelemer caused an approximate 30% reduction in the incidence and severity of diarrhea associated with daily oral administration of neratinib, which was statistically significant. Crofelemer also demonstrated significant improvement in the proportion of responder dogs, and there was a trend for fewer neratinib dose reductions in both crofelemer treatment groups when compared to the control group."

"Crofelemer is undergoing development for a potential additional indication of symptomatic relief of cancer therapy-related diarrhea (CTD)," Lisa Conte, Jaguar's president and CEO, stated. We are very excited about these preclinical results and are planning a pivotal trial in CTD patients to evaluate the effects of crofelemer in prevention and/or relief of CTD. Many patients on TKIs require drug holidays or dose reductions in their therapy due to diarrhea. Reduced frequency and severity of diarrhea will allow better maintenance to the therapeutic dose and dosing of any targeted therapies, potentially leading to better clinical outcomes. As we've learned from business development discussions with cancer agent manufacturers, adoption and continued use of TKIs and other targeted cancer therapies is directly related to the ability of patients to tolerate use of the therapies - highlighting the importance of supportive care to help manage treatment-related diarrhea in this patient population."

Dogs in all treatment groups received oral neratinib in the form of one 40 milligram tablet of neratinib for the first five days, which was then escalated from day six onwards to two tablets of neratinib, or 80 milligrams of neratinib once daily for the remainder of the study. Concomitant with the daily neratinib dosing, dogs in the three treatment groups received either placebo capsules or crofelemer (Mytesi) tablets twice a day (BID) or four times a day (QID).

Dogs with mild or moderate dehydration were given fluids as needed and/or a drug holiday of neratinib for reduction of severe diarrhea. No dogs in any treatment group during the study received loperamide to reduce the incidence or severity of diarrhea.

Three of the eight dogs in the control group were found to be "clinical responders" defined as dogs having ≤7 watery stools per week for 50% of the 28-day dosing period. In contrast, seven of eight dogs treated with oral neratinib and crofelemer QID were responders ($p = 0.02$), and six of eight dogs treated with oral neratinib and crofelemer BID were responders ($p = 0.03$), both of which were significantly higher than the control group.

Compared to placebo-treated dogs, the average number of watery stools per week was significantly less for both the crofelemer QID and crofelemer BID treatment groups during Week 1 as well as throughout the entire four-week treatment period.

Over the entire 28-day treatment period, dogs receiving placebo had an approximately 33% higher average number of watery stools when compared to dogs randomized to the crofelemer BID or QID groups ($p < 0.05$).

Stool consistency, as measured by the average fecal scores per week, demonstrated that dogs in the crofelemer QID treatment group ($p = 0.010$) and in the crofelemer BID treatment group ($p = 0.033$) had significantly more formed stools compared to the control group dogs.

When compared to placebo-treated dogs, there was a significant reduction in the average number of watery stools per neratinib tablet for both crofelemer treatment groups during Week 1 as well as over the entire 28-day treatment period.

Finally, stool consistency as measured by the average fecal scores per week per neratinib tablet showed significantly more formed stools for the crofelemer QID and BID groups over the entire 28-day treatment period compared to the control group.

**About Jaguar Health, Inc.**

Jaguar Health, Inc. is a commercial stage pharmaceuticals company focused on developing novel, plant-based, sustainably derived gastrointestinal products on a global basis. Our wholly owned subsidiary, Napo Pharmaceuticals, Inc., focuses on developing and commercializing proprietary plant-based human gastrointestinal pharmaceuticals for the global marketplace from plants used traditionally in rainforest areas. Our Mytesi® (crofelemer) product is approved by the U.S. FDA for the symptomatic relief of noninfectious diarrhea in adults with HIV/AIDS on antiretroviral therapy and the only oral plant-based prescription medicine approved under FDA Botanical Guidance.

For more information about Jaguar, please visit https://jaguar.health. For more information about Napo, visit www.napopharma.com.

**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 press release constitute "forward-looking statements." These include statements regarding the development of crofelemer for the potential additional indication of symptomatic relief of CTD, and the expectation that reduced frequency and severity of diarrhea will allow better maintenance to the therapeutic dose and dosing of any targeted therapies in cancer patients, potentially leading to better clinical outcomes. 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 release 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 release 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. Some of the factors that could affect our actual results are included in the periodic reports on Form 10-K and Form 10-Q that we file with the Securities and Exchange Commission. 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.

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