Dog Study Published in PLOS ONE Shows Statistically Significant Results for Use of Jaguar Health's Crofelemer for Preventive Treatment of Cancer Therapy-Related Diarrhea (CTD)

January 25, 2024

This study, conducted by Jaguar family company Napo Pharmaceuticals in collaboration with Puma Biotechnology, is one of three important studies providing scientific rationale for the use of crofelemer for prevention and treatment of CTD

Studies published in peer-reviewed journals and continuum of datapoints highlight the neglected and growing need for treatment of one of the most common and debilitating side effects of patients undergoing cancer therapy

SAN FRANCISCO, CA / ACCESSWIRE / January 25, 2024 / Jaguar Health, Inc. (NASDAQ:JAGX) today announced that a dog study evaluating the effects of crofelemer in providing symptomatic relief of diarrhea associated with the irreversible pan-human epidermal growth factor receptor (HER) tyrosine kinase inhibitor (TKI) neratinib (Nerlynx®) has been published in the peer-reviewed journal *PLOS ONE*. The study, titled *Effects of orally administered crofelemer on the incidence and severity of neratinib-induced diarrhea in female dogs*, was conducted by Jaguar family company Napo Pharmaceuticals in collaboration with Puma Biotechnology, Inc. and can be viewed by clicking **here**.

"We are very pleased with the results of this prophylactic study, which was undertaken to 'model' the human situation with neratinib," said Lisa Conte, Jaguar's president and CEO. "Crofelemer, our novel, oral, plant-based, non-opioid antidiarrheal prescription medication, is also the subject of OnTarget, Jaguar's pivotal Phase 3 clinical trial for the follow-on indication of the preventative treatment of cancer therapy-related diarrhea (CTD), an indication we also refer to as chemotherapy-induced overactive bowel (CIOB) - which includes symptoms such as unpredictable and/or chronic debilitating diarrhea and GI urgency. Diarrhea, which has the potential to cause dehydration, infections, and non-adherence to treatment in cancer patients, is a growing unmet medical need in the age of targeted cancer therapies."

Conte added, "This neratinib study was the first of three studies over the past several years that provide scientific rationale for the use of crofelemer in humans for treatment of CTD. This continuum of datapoints highlights the neglected and growing need for prophylaxis of diarrhea in cancer patients. Prophylactic therapies exist to help prevent chemotherapy-induced nausea and vomiting (CINV) in cancer patients, but no antidiarrheal medications are currently approved for treatment of CTD. Interestingly, there is currently one available product for diarrhea in dogs undergoing cancer treatment: Canalevia®-CA1 (crofelemer delayed-release tablets), our FDA conditionally approved prescription drug for the treatment of chemotherapy-induced diarrhea (CID) in dogs."

Effects of orally administered crofelemer on the incidence and severity of neratinib-induced diarrhea in female dogs

"This 28-day preclinical pharmacological study in healthy female dogs was designed to evaluate the scientific rationale for the use of crofelemer in humans in reducing the severity and incidence of diarrhea associated with a tyrosine kinase inhibitor (neratinib)," said Dr. Michael Guy, D.V.M., M.S., 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."

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.

"Diarrhea was reported in 95% of Nerlynx-treated patients in ExteNET, a randomized placebo-controlled trial in the extended adjuvant setting who were not required to receive antidiarrheal prophylaxis," said Dr. Guy. "Nerlynx dose reductions due to diarrhea are often needed, and patients are advised to initiate antidiarrheal prophylaxis. Unlike crofelemer, which is already approved for a chronic use, synthetic antidiarrheal antimotility drugs are opioids and can bring risks in higher doses, often lead to constipation, and are thus not suitable for long-term use."

Crofelemer for the Management of Neratinib-Associated Diarrhea in Patients With HER2+ Early-Stage Breast Cancer

This independent pilot phase 2 study, which was published in the peer reviewed journal *Clinical Breast Cancer* in October 2023, can be viewed by clicking **here**. The study results indicate that crofelemer may be effective for the management of neratinib-induced diarrhea.

"Seven patients underwent treatment with crofelemer and loperamide in this study, 5 of whom were able to control diarrhea with crofelemer alone. Though this study involved a small number of patients, the results show activity of crofelemer for the management of neratinib-induced diarrhea, which warrants further investigation of crofelemer for treatment of cancer therapy-related diarrhea (CTD)," said study investigator Hope S. Rugo, MD, Professor of Medicine and Winterhof Family Professor of Breast Oncology, University of California San Francisco Helen Diller Family Comprehensive

Cancer Center. Dr. Rugo is a member of Jaguar's Scientific Advisory Board.

This single center, open label trial enrolled patients with Stage 2 to 3 HER2+ breast cancer receiving neratinib in the extended adjuvant setting. One cohort took prophylactic crofelemer 125 mg BID and loperamide in the first 2 cycles, and as needed in the subsequent cycles. The second cohort received escalating doses of neratinib with loperamide. The primary endpoint was incidence of grade ≥3 diarrhea in the first 2 cycles.

HALT-D: A Randomized Open-Label Phase II Study of Crofelemer for the Prevention of Chemotherapy-Induced Diarrhea in Patients with HER2-Positive Breast Cancer Receiving Trastuzumab, Pertuzumab, and a Taxane

This investigator-initiated study, which was published in the peer reviewed journal *Breast Cancer Research and Treatment* in October 2022 and funded with support from Genentech, Inc., a member of the Roche group, can be viewed by clicking **here**. The targeted cancer therapies evaluated in the study cause diarrhea in up to 80% of breast cancer patients, reaching grade 3, which often requires hospitalization, in 8-12% of patients.

"Diarrhea is a debilitating side effect that many people experience when undergoing breast cancer treatment that demands research attention," said the study's senior investigator, Sandra M. Swain, MD, professor of medicine at Georgetown University and a member of its Lombardi Comprehensive Cancer Center. "This is one of few studies to explore ways of proactively preventing diarrhea in women undergoing lifesaving treatment for their breast cancer. While we have more work to do, this study revealed important information about the treatment of diarrhea in this particular population."

The results of the HALT-D study were released previously by the investigators at the 2021 San Antonio Breast Cancer Symposium by lead study investigator Paula Pohlmann, MD, PhD, formerly from Georgetown University and now Associate Professor, MD Anderson Cancer Center. HALT-D included 51 breast cancer patients scheduled to receive at least three cycles of chemotherapy and randomly assigned to either crofelemer in cycles 1 and 2 or the control group, which received standard of care. Antidiarrheal medications for breakthrough diarrhea were permitted but not given prophylactically.

REMINDER: Multinational Association of Supportive Care in Cancer (MASCC) Webinar on January 29, 2024

A Multinational Association of Supportive Care in Cancer (MASCC) webinar titled "GI Toxicities from Cancer Therapies - Prevention and Management" is taking place Monday, January 29, 2024 from 11:30 AM to 12:30 PM Eastern Standard Time. The webinar was made possible by an unrestricted educational grant from Jaguar family company Napo Pharmaceuticals. To register for the webinar, click here. MASCC does not endorse or promote products or services of any industry partner including Jaguar Health, Inc.

About Cancer Therapy-Related Diarrhea (CTD)

More than 1.9 million people were expected to be diagnosed with cancer in 2023 in the U.S., according to the American Cancer Society. A significant proportion of patients undergoing cancer therapy experience diarrhea, and diarrhea has the potential to cause dehydration, infections, and non-adherence to treatment in this population. Novel "targeted cancer therapy" agents, such as epidermal growth factor receptor (EGFR) antibodies and tyrosine kinase inhibitors (TKIs), with or without cycle chemotherapy agents, may cause increased electrolyte and fluid content in the gut lumen, which results in passage of loose/watery stools (i.e., diarrhea). Diarrhea has been reported as one of the most common side effects of TKIs and may result in cancer therapy drug holidays or reductions from therapeutic dose, potentially impacting patient outcome. Diarrhea is also a common side effect of some approved CDK 4/6 inhibitors. Patients with CTD are 40% more likely to discontinue their chemotherapy or targeted therapy than patients without CTD,[1] and the cost of care of CTD patients is estimated to be 2.9 times higher than for patients who are not experiencing CTD.[2]

About the Jaguar Health Family of Companies

Jaguar Health, Inc. (Jaguar) is a commercial stage pharmaceuticals company focused on developing novel proprietary prescription medicines sustainably derived from plants from rainforest areas for people and animals with gastrointestinal distress, specifically associated with overactive bowel, which includes symptoms such as chronic debilitating diarrhea, urgency, bowel incontinence, and cramping pain. Jaguar family company Napo Pharmaceuticals focuses on developing and commercializing human prescription pharmaceuticals for essential supportive care and management of neglected gastrointestinal symptoms across multiple complicated disease states. Napo Pharmaceuticals' crofelemer drug product candidate is the subject of the OnTarget study, a pivotal Phase 3 clinical trial for preventive treatment of chemotherapy-induced overactive bowel (CIOB) in adults with cancer on targeted therapy. Jaguar family company Napo Therapeutics is an Italian corporation Jaguar established in Milan, Italy in 2021 focused on expanding crofelemer access in Europe and specifically for orphan and/or rare diseases. Jaguar Animal Health is a Jaguar tradename. Magdalena Biosciences, a joint venture formed by Jaguar and Filament Health Corp. that emerged from Jaguar's Entheogen Therapeutics Initiative (ETI), is focused on developing novel prescription medicines derived from plants for mental health indications.

For more information about:

Jaguar Health, visit https://jaguar.health

Napo Pharmaceuticals, visit www.napopharma.com

Napo Therapeutics, visit napotherapeutics.com

Magdalena Biosciences, visit magdalenabiosciences.com

Visit Jaguar on LinkedIn: https://www.linkedin.com/company/jaguar-health/

Visit Jaguar on X: https://twitter.com/Jaguar_Health

Visit Jaguar on Instagram: https://www.instagram.com/jaguarhealthcommunity/

About Canalevia®-CA1

Canalevia-CA1 (crofelemer delayed-release tablets) is the first and only oral plant-based prescription product that is FDA conditionally approved to treat chemotherapy-induced diarrhea (CID) in dogs. Canalevia-CA1 is a canine-specific formulation of crofelemer, an active pharmaceutical ingredient isolated and purified from the *Croton lechleri* tree. Canalevia-CA1 is currently conditionally approved by the FDA under application number 141-552.

Conditional approval allows for commercialization of the product while Jaguar continues to collect the substantial evidence of effectiveness required for a full approval. Jaguar has received Minor Use in a Major Species (MUMS) designation from the FDA for Canalevia-CA1 to treat CID in dogs. FDA has established a "small number" threshold for minor use in each of the seven major species covered by the MUMS act. The small number threshold is currently 80,000 for dogs, representing the largest number of dogs that can be affected by a disease or condition over the course of a year and still have the use qualify as a minor use.

Important Safety Information About Canalevia®-CA1

For oral use in dogs only. Not for use in humans. Keep Canalevia-CA1 (crofelemer delayed-release tablets) in a secure location out of reach of children and other animals. Consult a physician in case of accidental ingestion by humans. Do not use in dogs that have a known hypersensitivity to crofelemer. Prior to using Canalevia-CA1, rule out infectious etiologies of diarrhea. Canalevia-CA1 is a conditionally approved drug indicated for the treatment of chemotherapy-induced diarrhea in dogs. The most common adverse reactions included decreased appetite, decreased activity, dehydration, abdominal pain, and vomiting.

Caution: Federal law restricts this drug to use by or on the order of a licensed veterinarian. Use only as directed. It is a violation of Federal law to use this product other than as directed in the labeling. Conditionally approved by FDA pending a full demonstration of effectiveness under application number 141-552.

Forward-Looking Statements

Certain statements in this press release constitute "forward-looking statements." These include statements regarding Jaguar's expectation that a MASCC webinar titled "GI Toxicities from Cancer Therapies - Prevention and Management" will take place January 29, 2024. 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 several 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.

[1] Pablo C. Okhuysen, M.D., The impact of cancer-related diarrhea on changes in cancer therapy patterns: Real world evidence

[2] Eric Roeland, M.D., FAAHPM, Healthcare utilization and costs associated with cancer-related diarrhea

Contact:

hello@jaguar.health

Jaguar-JAGX

SOURCE: Jaguar Health, Inc.