Jaguar Health Provides Corporate Update and Outlines 2022 Milestones

January 13, 2022

2021 was a year of progress for Jaguar Health as the company advanced its key human pipeline initiatives focused on chemotherapy-related diarrhea (CTD) and short bowel syndrome with intestinal failure (SBS-IF) and received conditional approval for Canalevia™-CA1 (crofelemer) for dogs

Pipeline advancing in 2022 with company's Phase 3 CTD study continuing and expected completion of an SBS-IF investigator-initiated proof-of-concept trial

2022: Jaguar's year of the dog with continued launch, education, and promotion activity for Canalevia-CA1, which received conditional approval December 21, 2021, for chemotherapy induced diarrhea in dogs

SAN FRANCISCO, CA / ACCESSWIRE / January 13, 2022 / Jaguar Health, Inc. (NASDAQ:JAGX) today provided a corporate update and outlined expected 2022 milestones.

"2021 was a year of progress for Jaguar Health as we advanced our key human pipeline initiatives with the presentation at December's San Antonio Breast Cancer Symposium of Phase 2 data for prophylaxis in chemotherapy-related diarrhea; received Orphan Drug Designation in the European Union for crofelemer for short bowel syndrome; formed Napo Therapeutics in Milan, Italy, which was subsequently funded as a result of the merger of Napo Therapeutics with Milan-based Dragon SPAC S.p.A. (with the funding referenced in Jaguar Health's October 25, 2021 press release); and completed a license agreement with Napo Therapeutics. In December we also excitingly and importantly received conditional approval for Canalevia™-CA1 for chemotherapy induced diarrhea in dogs," saidLisa Conte, Jaguar Health's president and CEO. "As we begin 2022, we look forward to an exciting year on the commercial front with our Canalevia-CA1 launch and continued sales of Mytesi®; the continued development of crofelemer - our 'pipeline within a product'; continuing efforts to forge license and business development relationships; and, most importantly, providing relief with a novel first-in-class mechanism of action to patients in need - including patients for whom no alternative therapeutic options exist."

2021 ACCOMPLISHMENTS & STATUS UPDATES:

Canalevia™-CA1: The First and Only Treatment for Chemotherapy-Induced Diarrhea (CID) in Dogs to Receive Any Type of Approval from the U.S. Food and Drug Administration (FDA)

Canalevia-CA1 (crofelemer delayed-release tablets) received conditional approval from the FDA on December 21, 2021. Canalevia-CA1 is being commercialized as a prescription drug product under the company's Jaguar Animal Health tradename. Canalevia-CA1 is a tablet that is given orally and can be prescribed for home treatment of CID.

The following quote appeared in the press release the FDA issued December 21, 2021: "Diarrhea is a common side effect of chemotherapy in dogs, which can be so severe that cancer treatment must be halted. Chemotherapy drugs often have potential side effects, but, unlike in human medicine where patients may be willing to tolerate some discomfort in exchange for a potential cure, the primary purpose of cancer treatment in dogs and other pets is to extend survival without sacrificing quality of life and comfort," said Steven M. Solomon, D.V.M., M.P.H., director of the FDA's Center for Veterinary Medicine. "This new medication provides veterinarians and dog owners with another tool to help control the side effects of chemotherapy for dogs undergoing such treatment."

The full FDA press release can be viewed by clicking here.

Due to the increasing number of chemotherapeutic agents being adopted by veterinarians and veterinary oncologists, chemotherapy is fast becoming the most widely used cancer treatment in veterinary medicine. Studies have found the incidence of CID to be one of the three most prevalent side effects in dogs undergoing cancer treatment[1], and managing side-effects such as diarrhea can be important to maintain successful cancer treatment. More than half of the U.S. veterinarians who responded to a recent Jaguar-sponsored survey reported that CID interferes with their patients' chemotherapy treatment plans, indicating an unmet need for an effective product for the treatment of CID.

Jaguar launched the www.canalevia.com website on December 22, 2021. For veterinarians, the site provides Canalevia-CA1 prescribing information, data on the pharmacological properties and novel mechanism of action of the product's active pharmaceutical ingredient, crofelemer, and a listing of upcoming veterinary conferences the company plans to attend. For dog owners, the site provides an overview of CID and its negative effects in dogs undergoing chemotherapy.

The company expects to conduct a number of educational and awareness-building activities for the U.S. dog community about the demographics of canine cancer and options for treatment and management of side effects of cancer therapy in dogs.

Cancer Therapy-related Diarrhea (CTD) in Humans

The pivotal **OnTarget** Phase 3 clinical trial of crofelemer for prophylaxis of diarrhea in adult cancer patients receiving targeted therapy was initiated in October 2020 by Napo Pharmaceuticals, Jaguar Health's wholly owned subsidiary, and is ongoing. Additional details about the trial can be viewed **here** on the clinicaltrials.gov website. The National Clinical Trial number for the trial is **NCT04538625**.

The third-party presentation of findings from the investigator-initiated HALT-D trial evaluating crofelemer for preventing chemotherapy-induced diarrhea (CID) in HER2-positive breast cancer patients being treated with trastuzumab, pertuzumab and a taxane took place December 10, 2021, at the San Antonio Breast Cancer Symposium. These therapies cause CID in up to 80% of breast cancer patients, reaching grade 3, which often requires hospitalization, in 8-12% of patients. No antidiarrheal medications are currently approved that specifically target the underlying mechanism of CID. The study results, presented by lead study investigator Paula Pohlmann, MD, PhD, formerly from Georgetown University and now Associate Professor, MD Anderson Cancer Center, provide the first proof-of-concept data for potential use of crofelemer in breast cancer patients.

A significant proportion of patients undergoing cancer therapy experience diarrhea, and diarrhea has the potential to cause dehydration, potential 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.

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. Findings showed that the primary endpoint, the incidence of diarrhea for at least two consecutive days, was not statistically different for the two groups. However, crofelemer patients demonstrated significantly better outcomes compared to control group patients across a number of key secondary endpoints in incidence and severity of diarrhea in cycle 2 based on Investigator and Patient Reported Outcomes (PRO). In the poster presentation, additional findings include that CID occurred significantly less (23%) in the crofelemer group during cycle 1 and crofelemer patients were 1.8 times more likely than control patients to have their diarrhea resolved.

The HALT-D data is expected to be submitted in early in 2022 by the study investigators for full journal publication.

Formation of Napo Therapeutics, the Exclusive Licensee of Crofelemer in Europe

Napo Therapeutics S.p.A. (formerly Known as Napo EU) is a European specialty drug development and marketing company based in Milan, Italy. Napo Therapeutics' mission is to provide access to crofelemer in Europe to address significant rare/orphan disease indications, including, initially, two key orphan target indications: Short bowel syndrome with intestinal failure (SBS-IF), and congenital diarrheal disorders (CDD).

Short Bowel Syndrome with Intestinal Failure (SBS-IF)

The European Medicines Agency (EMA) on December 10, 2021, granted Orphan Drug Designation (ODD) for crofelemer to Napo Therapeutics for short bowel syndrome (SBS). Recognition of ODD in Europe for crofelemer for this rare disease is the first key Napo Therapeutics milestone under the company's exclusive license agreement with Jaguar Health.

"With this very welcome decision from the EMA, Napo Therapeutics collaborated with Jaguar to host an important KOL session to inform efforts to plan and commence a pivotal clinical trial of crofelemer in both adult and pediatric SBS patients. We have also participated in discussions related to investigator-initiated trial (IIT) requests for an SBS proof-of-concept (POC) trial in 2022. We will support programs and requests for expanded patient access, likely to arise from the POC IIT. Our key focus is to provide a novel, safe, effective and compassionate alternative for patient care for this debilitating rare disease," said Massimo Mineo, General Manager of Napo Therapeutics.

SBS affects approximately 10,000 to 20,000 people in the U.S.[2], according to the Crohn's & Colitis Foundation, and it is estimated that the population of SBS patients in Europe is approximately the same size.[3] Despite limited treatment options, the global SBS market exceeded $568 million in 2019 and is expected to reach $4.6 billion by 2027, according to a report by Vision Research Reports.

"SBS is a devastating disease. The mortality rate of SBS patients on home parenteral nutrition is about 30% after 5 years[4], and it is estimated that approximately 70% of SBS patients in Europe are pediatric," said Lisa Conte, who is also Napo Therapeutics' chairman of the board. "The accelerated approval regulatory pathway in Europe is key to our strategy underlying the exclusive license Jaguar Health has provided to Napo Therapeutics for crofelemer and to our efforts to make crofelemer's novel mechanism of action available to patients suffering from rare diseases like SBS in the most rapid manner. Additionally, Jaguar Health has the right to utilize any clinical or regulatory data generated by Napo Therapeutics for SBS on a global basis, which provides us with another potential and important ‘shot on goal' for crofelemer."

Crofelemer previously received ODD in the U.S. from the FDA for SBS.

Jaguar also holds a majority equity stake in Napo Therapeutics, providing the opportunity to unlock and realize the value of Napo Therapeutics' rare disease-focused business model.

EXPECTED 2022 MILESTONES:

Ongoing Commercial Launch Activities for Canalevia-CA1

The company received the first purchase order for Canalevia-CA1 at the end of December and the product is already available from leading veterinary distributors in the U.S. Under its Jaguar Animal Health tradename for the veterinary market, the company is exhibiting at the veterinary conferences listed below. At both VMX and WVC, Jaguar Animal Health is hosting a CID Treatment Forum for veterinarians, veterinary oncologists, and members of the media.

- January 15-19, 2022: **Veterinary Meeting & Expo (VMX)**: Orlando, FL
- March 6-9, 2022: **Annual Western Veterinary Conference (WVC)**: Las Vegas

- April 9-12, 2022: **Veterinary Cancer Society (VCS) Mid-Year Conference**: Puerto Vallarta, Mexico
- June 23-25, 2022: **American College of Veterinary Internal Medicine (ACVIM) Forum**: Austin, TX

Mid-2022: Filing of an Investigational New Drug (IND) Application with the FDA for NP-300 (Lechlemer) in Support of Initiation of a Phase 1 Lechlemer Study in 2H 2022 for the Symptomatic Relief of Diarrhea from Cholera

Lechlemer is the company's drug product candidate for symptomatic relief of diarrhea from cholera. It is a standardized and proprietary Napo Pharmaceuticals botanical drug product that is sustainably derived from the same source as crofelemer - the *Croton lechleri* tree. Lechlemer development is planned to be conducted under FDA botanical guidance. In support of the planned IND application filing for lechlemer, the company received comprehensive animal toxicity preclinical services supported by the National Institute of Allergy and Infectious Diseases for four preclinical studies.

Cholera is an acute diarrheal illness caused by infection of the intestine with the bacterium Vibrio cholerae. According to the Centers for Disease Control and Prevention of the U.S. Department of Health & Human Services, an estimated 3-5 million cholera cases and more than 100,000 cholera-related deaths occur each year around the world. Jaguar Health believes that lechlemer, which has the same mechanism of action as crofelemer and is significantly less costly to produce, may, upon approval, be a candidate to receive a tropical disease priority review voucher from the FDA for an indication for the symptomatic relief of diarrhea from cholera. Priority Review Vouchers are transferable and, in past transactions by other companies, have sold for prices ranging from $67 million to $350 million.

Mid-2022: Initiation of a Proof-of-Concept Study of Crofelemer for the Congenital Diarrheal Disorders (CDD) Orphan Indication

The company expects the initiation of a proof-of-concept study of crofelemer for this rare disease indication in sites in the U.S. and Middle East in mid-2022. 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, and 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.

Q3 2022: Conditional Approval and Launch of Canalevia-CA2 for Exercise-Induced Diarrhea (EID) in Dogs

Jaguar Animal Health is seeking conditional approval from the FDA to market Canalevia (under the name Canalevia-CA2) for the treatment of exercise-induced diarrhea (EID) in dogs. Working dogs, including search and rescue, military, and sled dogs, often suffer diarrhea as a result of engaging in long periods of intense, off-leash exercise. There is a significant need in the world of working dogs for a safe and effective medicine that can reduce the incidence and severity of EID without affecting performance.

2H 2022: Initiation and Completion of investigator-initiated Proof-of-Concept Study of Crofelemer for SBS-IF

Napo Therapeutics expects to support this investigator-initiated proof-of-concept study in patients suffering from SBS. The planned primary endpoint for clinical trials of crofelemer in SBS-IF will be reduction of weekly volume of parenteral nutrition.

Investigator-Initiated Trials of Crofelemer That Are Ongoing in 2022:

- Chronic Idiopathic Diarrhea in Non-HIV Adult Patients
  - Study Name: *Yield of Diagnostic Tests and Management of Crofelemer for Chronic Idiopathic Diarrhea in Non-HIV Patients: A Pilot Study*
  - Location: University of Texas Health Science Center at Houston
- Functional Diarrhea in Non-HIV Adult Patients
  - Study Name: A randomized, double-blind, placebo-controlled study to evaluate the safety, tolerability, and efficacy of crofelemer in subjects with functional diarrhea
  - Location: Beth Israel Deaconess Medical Center, a Harvard Medical School institution in Boston

About Crofelemer

Crofelemer is a novel, oral plant-based medicine extracted and purified from the red bark sap, also referred to as "dragon's blood," of the medicinal *Croton lechleri* tree in the Amazon Rainforest. Jaguar Health's wholly owned subsidiary, Napo Pharmaceuticals, has established a sustainable harvesting program, under fair trade practices, for crofelemer to ensure a high degree of quality, ecological integrity, and support for Indigenous communities. Additionally, crofelemer is the active ingredient in an antidiarrheal that is approved by the FDA under botanical guidance and indicated for the symptomatic relief of noninfectious diarrhea in adult human patients with HIV/AIDS on antiretroviral therapy and in Canalevia™-CA1, which is conditionally approved for chemotherapy-induced diarrhea in dogs.

About Jaguar Health, Inc., Jaguar Animal Health, Napo Pharmaceuticals, Inc. & Napo Therapeutics S.p.A.

Jaguar Health, Inc. is a commercial stage pharmaceuticals company focused on developing novel, plant-based, non-opioid, and sustainably derived prescription medicines for people and animals with GI distress, specifically chronic, debilitating diarrhea. Jaguar Animal Health is a tradename of Jaguar Health. Jaguar Health's wholly owned subsidiary, Napo Pharmaceuticals, Inc., focuses on developing and commercializing proprietary plant-based human gastrointestinal pharmaceuticals from plants harvested responsibly from rainforest areas. Napo Therapeutics S.p.A., the majority owned Italian subsidiary of Napo Pharmaceuticals, focuses on expanding crofelemer access in Europe.

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

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 Health's expectation that it will conduct a number of educational and awareness-building activities for the U.S. dog community about the demographics of canine cancer and options for treatment and management of side effects of cancer therapy in dogs, the expectation that HALT-D data will be submitted in early 2022 by the study investigators for full journal publication, the expectation that the global SBS market will reach $4.6 billion by 2027, Jaguar Health's expectation that the majority equity stake it holds in Napo Therapeutics provides the opportunity to unlock and realize the value of Napo Therapeutics' rare disease-focused business model, the expectation that Jaguar Animal Health will exhibit at the 2022 VMX, WVC, VCS and ACVIM conferences and conduct CID Treatment Forums at certain conferences, the expectation that an IND Application will be filed with the FDA for lechlemer in mid-2022 and that a Phase 1 lechlemer study for the symptomatic relief of diarrhea from cholera will be initiated in the second half of 2022, the expectation that lechlemer development will be conducted under FDA botanical guidance, the expectation that lechlemer may, upon approval, be a candidate to receive a tropical disease priority review voucher from the FDA for an indication for the symptomatic relief of diarrhea from cholera, the expectation that initiation of a proof-of-concept study of crofelemer for CDD will take place in mid-2022 at sites in the U.S. and Middle East, the expectation that the conditional approval and launch of Canalevia-CA2 for EID in dogs will take place in the third quarter of 2022, and the expectation that the initiation and completion of an investigator-initiated proof-of-concept study of crofelemer for SBS-IF will take place in the second half of 2022. 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.

[1] Mason SL, Grant IA, Elliott J, Cripps P, Blackwood L. Gastrointestinal toxicity after vincristine or cyclophosphamide administered with or without maropitant in dogs: a prospective randomized controlled study. *J Small Anim Pract*. 2014;55:391-398

[2] http://www.crohnscolitisfoundation.org/sites/default/files/legacy/assets/pdfs/short-bowel-disease-crohns.pdf

[3] http://www.pharmabiz.com/NewsDetails.aspx?aid=84221&sid=2

[4] Schalamon J, Mayr JM, Höllwarth ME. Mortality and economics in short bowel syndrome. *Best Pract Res Clin Gastroenterol*. 2003;17(6):931-942. doi:10.1016/s1521-6918(03)00079-9

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