Jaguar Health, Inc.
Form 10-K
April 10, 2019
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UNITED STATES

SECURITIES AND EXCHANGE COMMISSION

Washington, DC 20549

Form 10-K

(Mark One)

ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934

For the fiscal year ended December 31, 2018

TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934

For the transition period from to

COMMISSION FILE NO. 001-36714

JAGUAR HEALTH, INC.

(Exact name of registrant as specified in its charter)

Delaware	46 2956775
(State or other jurisdiction of incorporation or organization)	(I.R.S. Employer Identification No.)

201 Mission Street, Suite 2375

San Francisco, California 94105

(Address of principal executive offices)

Registrant's telephone number, including area code:

(415) 371 8300

SECURITIES REGISTERED PURSUANT TO SECTION 12(b) OF THE ACT:

Title of each class	Name of each exchange on which registered
Common Stock, Par Value $0.0001 Per Share	The NASDAQ Capital Market

SECURITIES REGISTERED PURSUANT TO SECTION 12(g) OF THE ACT: None

Indicate by check mark if the registrant is a well-known seasoned issuer, as defined in Rule 405 of the Securities Act. Yes No

Indicate by check mark if the registrant is not required to file reports pursuant to Section 13 or 15(d) of the Act. Yes No

Indicate by check mark whether the registrant: (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days. Yes No

Indicate by check mark whether the registrant has submitted electronically every Interactive Data File required to be submitted pursuant to Rule 405 of Regulation S-T during the preceding 12 months (or for such shorter period that the registrant was required to submit such files). Yes No

Indicate by check mark if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K is not contained herein, and will not be contained, to the best of registrant's knowledge, in definitive proxy or information statements incorporated by reference in Part III of this Form 10-K or any amendment to this Form 10-K.

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, a smaller reporting company, or an emerging growth company. See the definitions of "large accelerated filer," "accelerated filer," "smaller reporting company," and "emerging growth company" in Rule 12b-2 of the Exchange Act.

Large accelerated filer	Accelerated filer	Non-accelerated filer	Smaller reporting company Emerging growth company

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act.

Indicate by check mark whether the registrant is a shell company (as defined in Rule 12b-2 of the Exchange Act). Yes No

As of June 30, 2018, the aggregate market value of the registrant's common stock held by non-affiliates was approximately $12,405,942 based upon the closing sales price of the registrant's common stock on The NASDAQ Global Market on such date.

The number of shares of the registrant's Common Stock outstanding as of April 5 was 59,415,042 shares of voting common stock and 40,301,237 shares of non-voting common stock. The company also had 5,524,926 shares of convertible preferred stock outstanding (convertible into 33,149,556 shares of voting common stock, subject to certain voting restrictions as provided in the Certificate of Designation for the convertible preferred stock).

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the proxy statement for the registrant's 2019 Annual Meeting of Stockholders, or Proxy Statement, to be filed within 120 days of the end of the fiscal year ended December 31, 2018 are incorporated by reference in Part III hereof. Except with respect to information specifically incorporated by reference in this Form 10-K, the Proxy Statement is not deemed to be filed as a part hereof.

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PART I

Forward looking statements

This Form 10 K contains forward looking statements within the meaning of Section 21E of the Securities Exchange Act of 1934, as amended, or the Exchange Act. All statements other than statements of historical facts contained in this Form 10 K, including statements regarding our future results of operations and financial position, business strategy, prospective products, product approvals, research and development costs, timing of receipt of clinical trial, field study and other study data, and likelihood of success, commercialization plans and timing, other plans and objectives of management for future operations, and future results of current and anticipated products are forward looking statements. These statements involve known and unknown risks, uncertainties and other important factors that may cause our actual results, performance or achievements to be materially different from any future results, performance or achievements expressed or implied by the forward looking statements.

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” o of these terms or other similar expressions. The forward looking statements in this Form 10 K are only predictions. We have based these forward looking statements largely on our current expectations and projections about future events and financial trends that we believe may affect our business, financial condition and results of operations. These forward looking statements speak only as of the date of this Form 10 K and are subject to a number of risks, uncertainties and assumptions described under the sections in this Form 10 K titled “Risk Factors” and “Management’s Discussion and Analysis of Financial Condition and Results of Operations” and elsewhere in this Form 10 K. Forward looking statements are subject to inherent risks and uncertainties, some of which cannot be predicted or quantified and some of which are beyond our control. The events and circumstances reflected in our forward looking statements may not be achieved or occur and actual results could differ materially from those projected in the forward looking statements. Moreover, we operate in a dynamic industry and economy. New risk factors and uncertainties may emerge from time to time, and it is not possible for management to predict all risk factors and uncertainties that we may face. Except as required by applicable law, we do 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.

Jaguar Health, our logo, Canalevia and Neonorm are our trademarks that are used in this Form 10 K. This Form 10 K also includes trademarks, tradenames and service marks that are the property of other organizations. Solely for convenience, trademarks and tradenames referred to in this Form 10 K appear without the ©, ® or ™ symbols, but those references are not intended to indicate that we will not assert, to the fullest extent under applicable law, our rights or that the applicable owner will not assert its rights, to these trademarks and tradenames.

ITEM 1. BUSINESS

BUSINESS

Overview

We are a commercial stage natural products pharmaceuticals company focused on developing novel, sustainably derived gastrointestinal products on a global basis. Our wholly owned subsidiary, Napo Pharmaceuticals, Inc. (“Napo”), focuses on developing and commercializing proprietary human gastrointestinal pharmaceuticals for the global marketplace from plants used traditionally in rainforest areas. Our Mytesi (crofelemer) product is approved by the

U.S. Food and Drug Administration ("FDA") for the symptomatic relief of noninfectious diarrhea in adults with HIV/AIDS on antiretroviral therapy.

Jaguar was founded in San Francisco, California as a Delaware corporation on June 6, 2013. Napo formed Jaguar to develop and commercialize animal health products. Effective as of December 31, 2013, Jaguar was a wholly owned subsidiary of Napo, and, until May 13, 2015, Jaguar was a majority owned subsidiary of Napo. On

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July 31, 2017, the merger of Jaguar Animal Health, Inc. and Napo became effective, at which point Jaguar Animal Health's name changed to Jaguar Health, Inc. and Napo began operating as a wholly owned subsidiary of Jaguar focused on human health and the ongoing commercialization of, and development of follow on indications for Mytesi. Most of the activities of the Company are now focused on the commercialization of Mytesi and development of follow-on indications for crofelemer and a second-generation anti-secretory product, lechlemer. In the field of animal health, we have limited activities which are focused on developing and commercializing first in class gastrointestinal products for dogs, dairy calves, foals, and high value horses.

We believe Jaguar is poised to realize a number of synergistic, value adding benefits—and an expanded pipeline of potential blockbuster human follow on indications of crofelemer, and a second generation anti secretory agent--upon which to build global partnerships. As previously announced, Jaguar, through Napo, now holds extensive global rights for Mytesi, and crofelemer manufacturing is being conducted at two FDA-inspected and approved locations, including a new, multimillion dollar commercial manufacturing facility. Additionally, several of the drug product candidates in Jaguar's Mytesi pipeline are backed by strong Phase 2 evidence from completed Phase 2 trials.

Mytesi is a novel, first in class anti secretory agent which has a basic normalizing effect locally on the gut, and this mechanism of action has the potential to benefit multiple disorders. Mytesi is in development for multiple possible follow on indications, including diarrhea related to targeted cancer therapy; orphan drug indications for infants and children with congenital diarrheal disorders and short bowel syndrome (SBS); supportive care for inflammatory bowel disease (IBD); irritable bowel syndrome (IBS); and for idiopathic/functional diarrhea. In addition, a second generation proprietary anti secretory agent, lechlemer, is in development for cholera. Mytesi has received orphan drug designation for SBS.

Napo has a direct sales force of 16 sales representatives, a national sales director and one regional sales director covering U.S. geographies with the highest potential. In June 2018, we hired Robert J. Griffing, a seasoned industry veteran with a broad range of experience that includes commercializing supportive care and HIV treatments, as chief commercial officer for Napo. With support provided by concomitant marketing, promotional activities, patient empowerment programs and medical education initiatives described below, we expect continued growth in the number of patients treated with Mytesi.

The goal of Napo's internal sales team is to deliver a frequent and consistent selling message to targeted, high-volume prescribers of antiretroviral therapies (ART) and to gastroenterologists who see large numbers of HIV patients. In December 2017 we released the results of a survey of 350 people living with HIV and AIDS regarding the topic of "Talking to Your Doctor About Symptoms". The survey results show that diarrhea remains prevalent in those living with HIV/AIDS, as 27% of respondents living with HIV/AIDS reported that they currently have diarrhea, while 56% reported that they have had diarrhea in the past. Additionally, the results of a recent Napo-sponsored survey of 271 U.S. board certified gastroenterologists indicate that the number one GI complaint for people living with HIV/AIDS is diarrhea, and 93% of U.S. gastroenterologists see patients with HIV/AIDS in their practice.

Key to the success of our sales representatives in growing Mytesi sales is differentiating and targeting the right doctors—those HIV specialists who are high prescribers of ART medications and those gastrointestinal doctors who see large populations of people living with HIV/AIDS. The target list of prescribers for our sales reps includes a pool of approximately 3,100 high volume ART prescribing HIV specialists, and gastroenterologists who see the largest number of people living with HIV/AIDs, and we've strategically placed our sales force in the US geographies with the highest potential, including San Francisco, southern California, Arizona, Nevada, Miami/southern Florida, northern Florida, New York City/Long Island, Massachusetts, Rhode Island, New Hampshire, Connecticut, New Jersey, northern Texas, southern Texas, Chicago, Alabama, Mississippi, Louisiana, North Carolina/South Carolina, Michigan, Indianapolis, Ohio and Atlanta.

In June 2018, Napo entered into an agreement with RedHill Biopharma, a specialty biopharmaceutical company primarily focused on late clinical-stage development and commercialization of proprietary drugs for gastrointestinal diseases and cancer, to establish a U.S. co-promotion program for Mytesi.

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RedHill's specialized, GI-focused field sales force is promoting Mytesi to health care practitioners in 36 U.S. territories that contain significant numbers of HIV patients and health care practitioners that are not currently covered by Napo's field sales force. In these geographies, RedHill sales representatives target gastroenterologists who see large populations of people living with HIV, along with nurse practitioners and physician assistants. RedHill field representatives also target lower-level prescribers of anti-retroviral infectious disease specialists in regions currently covered by Napo's sales force. Four RedHill inside sales representatives actively target health care practitioners in other regions not covered by the Napo or RedHill field representatives. We believe this copromotion program will play an important role in extending the reach of our commercial efforts into the GI medical community in support of the treatment of people living with HIV (PLWH) with Mytesi. Under the terms of the Agreement, RedHill is compensated based on performance, and the program can be extended by agreement between the two companies , as it was in January 2019.

Medical education presentations led by health care practitioners (HCPs) participating in the Napo Speakers Bureau—a group that includes HIV/AIDS specialists, infectious disease specialists, gastroenterologists, colorectal surgeons, and nurse practitioners—focus on the prevalence and pathophysiology of gastrointestinal consequences of HIV infection and on the latest treatment options for HIV-related diarrhea. Presentations given by patient advocate members provide information to PLWH about the prevalence of diarrhea in PLWH and offer guidance about talking to HCPs regarding diarrhea-related concerns.

On July 24, 2018, we announced the results of an analysis conducted to examine whether the rate of HIV-associated diarrhea has changed over time. The analysis of data, sourced from the National Institutes of Health (NIH) clinicaltrials.gov database, revealed that 18% of HIV patients experience diarrhea and the rates have not declined significantly over time. The analysis includes data from 38 U.S. clinical trials from 2008-2016 in more than 21,000 patients. The results were reported at the International AIDS 2018 Conference (AIDS 2018) on Tuesday, July 24 in Amsterdam, Netherlands. The poster is available on the AIDS 2018 website at this link: https://programme.aids2018.org//PAGMaterial/eposters/4900.pdf.

With the introduction of newer antiretroviral (ARV) drug therapy, there has been a reduction in the severity of ARV-induced diarrhea. However, a significant portion of this patient population still suffers from diarrhea caused by HIV enteropathy, which is due to direct and indirect effects of HIV on the intestinal mucosa. Chronic diarrhea remains a significant complaint of people living with HIV/ AIDS, particularly those who are older and have lived with the virus in their gut for 10+ years. According to data from the U.S. Centers for Disease Control and Prevention, currently more than 50% of people living with HIV are over age 50; by 2020 this figure will increase to 70%.

Crofelemer (Mytesi) data from a supplemental analysis of the ADVENT trial was featured in a poster presentation at the 9th International Aids Society (IAS) Conference on HIV Science held in July 2017 in Paris, France. The presentation was titled Long-Term Crofelemer Use Gives Clinically Relevant Reductions in HIV-Related Diarrhea. IAS features the latest HIV science, including basic, clinical and prevention research, and brings together a broad cross section of HIV professionals from around the world with a focus on implementation—moving scientific advances into practice. The results indicate that at the end of the study period, more than 50% of the patients treated had complete resolution of their diarrhea; and 83% had at least a 50% reduction in diarrhea. Entry criteria required at least 7 watery stools in a week, and the average was 20 (with some patients having as high at 67 stools in a week).

Napo continues to pursue AIDS Drug Assistance Program (ADAP) formulary listing. ADAPs provide life-saving HIV treatments to low income, uninsured, and underinsured individuals living with HIV/AIDS in all 50 states and the territories. The ADAP program provides Mytesi free of charge to patients who qualify and copay support for some patients who have insurance coverage. In the third quarter of 2018, Mytesi was added to the ADAP formularies in New York, Tennessee, Mississippi and DC. As announced January 24, 2019, Mytesi has also been added to the formulary for Florida's ADAP, which is the third largest in the U.S. based on enrollment. As a result of this addition,

based on data from healthcare research firm Decision Resource Group, approximately 86% of ADAP-eligible US lives now have access to Mytesi, which is now on the ADAP formularies for 30 states, including the five programs with the largest enrollment.

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As we announced April 10, 2018, Napo has signed an agreement with the ADAP Crisis Task Force. The agreement establishes a reduced price provided by Napo ADAPs in all U.S. states and territories for purchases of Mytesi. Formed in 2002, the Task Force negotiates reduced drug prices for all ADAPs. Task Force membership is currently comprised of representatives from Arizona, California, Florida, Illinois, Massachusetts, New York, North Carolina, Tennessee, Texas, Virginia, and Washington state HIV/AIDS divisions. Per the terms of the agreement, all state ADAPs are guaranteed the same reduced price for the drug. ADAPs provide HIV-related services and approved medications to more than half a million people in the U.S. each year, and we expect this agreement to help further expand the number of patients able to benefit from the novel, first-in-class anti-secretory mechanism of action of Mytesi.

Mytesi is currently reimbursed by Medicaid in all 50 states. It is also currently covered on 100% of the top 10 commercial insurance plan national formularies, representing more than 245 million U.S. lives. Additionally, Napo operates a co-pay coupon program, which helps ensure that the majority of participating patients do not have a Mytesi co-pay greater than $25. Information about the NapoCares Patient Assistance Program, which assists patients with benefit verification, prior authorization, and claims appeals, can be found at mytesi.com/mytesi-savings.html.

Pipeline within a product—crofelemer

According to the World Health Organization, there are nearly 1.7 billion cases of diarrheal disease globally every year. Although not all types of diarrhea are secretory in nature, we view the current, initial approval of Mytesi as the opening of the door to an important pipeline—underscored by the current approval by the FDA of the Chemistry, Manufacturing and Controls (CMC) for this natural product, as well as acknowledgement by the FDA of the safety of the product for chronic use for the approved indication.

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

Our planned study for diarrhea related to CTD is analogous to the successful pivotal program we ran for Mytesi's currently approved HIV indication, and as part of risk mitigation we intend to use the same formulation and dosing as the current commercialized Mytesi. As part of Jaguar's near-term plan, Jaguar had a meeting with the FDA in March 2019 to discuss the anticipated protocol for a planned pivotal trial for the evaluation of crofelemer in CTD. The meeting, which included academic key opinion leaders (KOLs)/Napo Scientific Advisory Board members from leading oncology treatment institutions, resulted in a productive regulatory discussion about design refinements for the anticipated pivotal trial.

There are two ongoing investigator initiated trials (IITs) utilizing Mytesi to address CTD. Enrollment is ongoing for the HALT D study at Georgetown University in breast cancer patients on treatment with Herceptin, which is being funded by Genentech Roche, and interim results are expected to be read out in the first half of 2019. The second study, which is funded by Puma, is evaluating the use of crofelemer in subjects receiving neratinib, which has extremely high rates of diarrhea.

According to data appearing in "Treatment Guidelines for CID" (chemotherapy induced diarrhea) in the April 2004 issue of Gastroenterology and Endoscopy News, diarrhea is the most common adverse event reported in chemotherapy patients. Approved third party supportive care products for chemotherapy induced nausea and vomiting (CINV) include Sustol, Aloxi, Akynzeo and Sancuso. According to Transparency Market Research, sales of therapeutics for the prevention of CINV approximated $620 million in 2013, and sales of such therapeutics are expected to reach $1 billion in 2020.

Diarrhea has been reported as the most common side effect of the recently approved CDK 4/6 inhibitor abemaciclib and the pan HER TKI neratinib, with occurrence ranging from 86% to >95% and grade 3 over 40%, in published studies. Diarrhea in this patient population has the potential to cause dehydration, potential infections, and

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non adherence to treatment. A novel anti diarrheal like Mytesi may hold promise for treating secretory diarrhea—and therefore also support long term cancer treatment adherence—in this population.

As we announced on January 22, 2018, Napo has accepted a request for support submitted by Dr. Mohamad Miqdady, Chief of Pediatric Gastroenterology, Hepatology and Nutrition at Sheikh Khalifa Medical City (SKMC) in Abu Dhabi, for an investigator initiated trial of crofelemer, the active pharmaceutical ingredient in Mytesi, for congenital diarrheal disorders (CDDs) in children.

CDDs are a group of rare, chronic intestinal channel diseases, 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 marriages (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 immediate therapy to prevent death and limit lifelong disability.

SKMC is the Abu Dhabi public health system's flagship institution and the largest hospital in the United Arab Emirates (UAE), consisting of a 586 bed tertiary hospital, 14 outpatient specialty clinics, and the Abu Dhabi Blood Bank, all of which are accredited by Joint Commission International, the oldest and largest healthcare standards setting and accrediting body in the United States. Dr. Miqdady is an American Board certified in Pediatric Gastroenterology, Hepatology and Nutrition, and he is a member of Napo's Scientific Advisory Board.

Napo intends to submit documentation in the first half of 2019 to the U.S. FDA for the planned formulation of crofelemer appropriate for feeding tube administration to support this investigation.

As announced on June 5, 2017, Napo has received orphan drug designation from the FDA for pediatric short bowel syndrome (SBS). The Orphan Drug Act provides for granting special status to a drug or biological product to treat a rare disease or condition upon request of a sponsor. Orphan drug designation qualifies the sponsor of the drug for various development incentives, including extended exclusivity, tax credits for qualified clinical testing, and relief of filing fees.

Jaguar's and Napo's portfolio development strategy involves meeting with Key Opinion Leaders (KOLs) to identify indications that are potentially high value because they address important medical needs that are significantly or globally unmet, obtain input on protocol practicality and protocol generation, and then strategically sequencing indication development priorities, second generation product pipeline development, and partnering goals on a global basis, as well as identifying possible opportunities for a Special Protocol Assessment (SPA) from the FDA. When granted, SPA provides that, upon request, FDA will evaluate within 45 days certain protocols to assess whether they are adequate to meet scientific and regulatory requirements identified by the sponsor. In 2007, under the SPA process, Napo obtained agreement with the FDA for the design of the pivotal study protocol for the currently approved indication of crofelemer (Mytesi) for the symptomatic relief of noninfectious diarrhea in adults with HIV/AIDS on antiretroviral therapy. The 2007 SPA agreement was an important milestone for Napo, allowing Napo to address and mitigate regulatory uncertainty prior to the completion of its final Phase 3 trial of crofelemer for its currently approved indication.

In October 2017, Napo established a scientific advisory board for each potential follow on indication currently planned for Mytesi. Napo has developed relationships with physicians and patient advocates around the world who are recognized specialists and key opinion leaders (KOLs) in the planned Mytesi follow on indications. The two charts below provide the names, credentials and affiliations of current Napo scientific advisory board members and KOL advisors to Napo.

We are confident that our scientific advisory boards will provide expert, actionable input regarding all aspects of development, including trial design, for Mytesi for our follow on indications—each of which addresses a significant, global, unmet medical need. We also expect that our scientific advisory board members will serve as speakers for our medical education programs, authors on Napo abstracts and publications, and as a resource for media inquiries.

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Napo's HIV Scientific Advisory Board has focused primarily on physician education, and community and global awareness regarding the importance and availability of solutions for neglected comorbidities, such as the first in class anti secretory mechanism of action of Mytesi for its currently approved indication.

Napo Scientific Advisory Board (SAB) Members

Pravin Chaturvedi, PhD	Chair of Napo's Scientific Advisory Boards; 25+ years drug development experience in pharmaceutical/biotech field; Successfully developed crofelemer (Mytesi) (first pivotal adaptive design)

HIV Physicians Scientific Advisory Board

David Asmuth, MD	Infectious diseases specialist and Professor of Medicine, UC Davis Health
Gary Blick, MD, AAHIVS	Founder of Health Care Advocates International and BEAT AIDS Project Zimbabwe
Christine Wanke, MD	Director of the Nutrition and Infection Unit; Associate Chair and Professor, Department of Public Health and Community Medicine; Professor, Department of Medicine, Tufts University School of Medicine; Professor, Sackler School of Biomedical Science; Professor, Friedman School of Nutrition Science and Policy

Cancer Therapy Related Diarrhea Scientific Advisory Board

Lee Schwartzberg, MD, FACP	Executive Director of the West Cancer Center, a multispecialty oncology practice affiliated with the University of Tennessee; Chief, Division of Hematology/Oncology, the University of Tennessee Health Science Center
Eric Roeland, M.D.	Attending Physician, Center for Palliative Care, Harvard Medical School
Hope Rugo, MD	Clinical Professor of Medicine, Director Breast Oncology and Clinical Trials Education, Division of Hematology and Oncology, University of California San Francisco

IBD Scientific Advisory Board

Corey Siegel, MD, MS	Associate Professor of Medicine; Associate Professor of The Dartmouth Institute; Director of the Inflammatory Bowel Disease Center at the Dartmouth Hitchcock Medical Center

Pediatric Indications (SBS and CDD) Scientific Advisory Board

Mohammed Miqdady, MD	Chief of Pediatric Gastroenterology, Hepatology & Nutrition at Sheikh Khalifa Medical City in Abu Dhabi

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Martin Martin, MD	Professor, Department of Pediatrics, David Geffen School of Medicine at UCLA
Sue Rhee, MD	Division Chief, Pediatric Gastroenterology, Hepatology and Nutrition Pediatric gastroenterologist and liver specialist, UCSF Benioff Children's Hospital

Key Opinion Leader (KOL) Advisors to Napo (on an as needed basis)

KOL Advisors: Cancer Therapy Related Diarrhea

Herbert DuPont, MD	Professor and Director, Center for Infectious Diseases, University of Texas Houston School of Public Health
Pablo C. Okhuysen, M.D.	Department of Infectious Diseases, Infection Control, and Employee Health, Division of Internal Medicine, MD Anderson

KOL Advisors: Diarrhea Related to IBD

David Rubin, MD	Joseph B. Kirsner Professor of Medicine Section Chief, Gastroenterology, Hepatology and Nutrition Co Director, Digestive Diseases Center, University of Chicago Medicine
Charles Bernstein, MD	Distinguished Professor of Medicine and Bingham Chair in Gastroenterology Research, University of Manitoba
William Sandborn, MD	Director, Inflammatory Bowel Disease Center Chief, Division of Gastroenterology Professor of Medicine, US San Diego Health
Scott Lee, MD	Associate Professor of Medicine, Digestive Health Center, University of Washington Medical Center
Edward Loftus, Jr., MD	Consultant, Division of Gastroenterology and Hepatology, Department of Internal Medicine, Mayo Clinic
Douglas Wolf, MD	Medical Director of IBD Research at Atlanta Gastroenterology Associates. Clinical Assistant Professor of Medicine, Emory University School of Medicine
Brooks D. Cash, MD, AGAF, FACG, FACP, FASGE	Division Director, Gastroenterology, Hepatology, and Nutrition Visiting Professor of Medicine, The University of Texas McGovern Medical School

KOL Advisors: Pediatric Indications (SBS and CDD)

Jay Thiagarajah, MD, PhD	Attending Physician, Division of Gastroenterology, Hepatology and Nutrition, Boston Children's Hospital. Instructor of Pediatrics, Harvard Medical School
James Goldenring, M.D., Ph.D.	Professor of Surgery, Vanderbilt University School of Medicine. Paul W. Sanger Chair in Experimental Surgery. Professor of Cell and Developmental Biology

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KOL Advisors: Diarrhea Related to HIV and other Infectious Diseases

Herbert DuPont, MD	Professor and Director, Center for Infectious Diseases, University of Texas Houston School of Public Health
Pradip Bardhan, MBBS, MD	Chief Physician at ICDDR,B, Bangladesh
Patrick Clay, Pharm D	Consultant
Paulo Pacheco, MD	Clinical Assistant Professor, Department of Medicine, New York University Langone Health
Elie Schochet, MD, FACS	Colorectal surgeon, Holy Cross Medical Group

KOL Advisors: Diarrhea Related to IBS

Anthony Lembo, MD	Director of the GI Motility and Functional Bowel Disorders Program at Beth Israel Deaconess Medical Center and Associate Professor of Medicine at Harvard Medical School
Doug Drossman, Co MD	Director Emeritus, UNC Center for Functional GI and Motility Disorders Adjunct Professor of Medicine and Psychiatry, University of North Carolina School of Medicine
William Chey, MD	Professor of Internal Medicine and Professor of Nutritional Sciences, University of Michigan School of Public Health

According to a 2017 report from Research and Markets, the combined global market for prescription and OTC gastrointestinal agents is expected to reach $21 billion by 2025. Jaguar estimates that a first in class anti secretory agent should be able to achieve a significant portion of the market share.

Our management team has significant experience in gastrointestinal product development for both humans and animals. Napo was founded 30 years ago to perform drug discovery and development by leveraging the knowledge of traditional healers working in rainforest areas. Ten members of the Jaguar and Napo team have been together for more than 15 years. Dr. Steven King, our executive vice president of sustainable supply, ethnobotanical research and intellectual property, and Lisa Conte, our founder, president and CEO, have worked together for more than 30 years. Together, these dedicated personnel successfully transformed crofelemer, which is extracted from trees growing in the rainforest, to Mytesi, which is a natural, sustainably harvested, FDA approved drug.

There are significant barriers to entry for Mytesi (crofelemer). Through Napo, we hold an extensive global patent portfolio. At the present time we hold approximately 142 issued worldwide patents, with coverage in many cases that extends until 2031. These issued patents cover multiple indications including HIV AIDS diarrhea, IBS, IBD, manufacturing, enteric protection from gastric juices, among others. We also have approximately 24 pending patent applications worldwide in the human health areas that are being prosecuted.

Mytesi is the first oral drug approved by the FDA under botanical guidance, which provides another barrier to entry from potential generic competition. The FDA requires that the manufacturer of crofelemer use a validated proprietary bioassay to release the drug substance and drug product of Mytesi. While most generic products are fashioned to meet chemical release specifications that are in the public domain, the specifics of this assay are not publicly available. There is no pathway by which a generic product can be developed for a drug approved under botanical guidance. In addition, Mytesi is not systemically absorbed, so the classic approach of creating a generic drug by

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matching pharmacokinetic blood levels is not possible. A generic player would have to conduct costly and risky clinical trials.

While Jaguar's commercial and development efforts have evolved to focus primarily on Mytesi and human pipeline indications since its merger with Napo, the Company is continuing limited initiatives related to Canalevia, its drug product candidate for treatment of chemotherapy induced diarrhea ("CID") in dogs, and Equilevia, its non prescription, personalized, premium product for total gut health in equine athletes. CID in dogs is typically caused by the same mechanism of action as in humans, and hence the work in dogs serves as a preclinical proof of concept for the diarrhea in humans that is related to targeted cancer therapy.

As previously announced, Jaguar has received MUMS (Minor Use and Minor Species) designation status from the FDA for Canalevia for the indication of CID in dogs. MUMS designation is modeled on the orphan drug designation for human drug development and offers possible financial incentives to encourage MUMS drug development, such as the availability of grants to help with the cost of developing the MUMS drug. Additionally, as announced on March 8, 2018, the FDA's Center for Veterinary Medicine (CVM) has indicated that Jaguar's Reasonable Expectation of Effectiveness (RxE) technical section is complete towards conditional approval of Canalevia. As announced March 20, 2019, Jaguar has completed the filing with CVM of the Chemistry, Manufacturing, and Controls (CMC) technical section in support of the Company's application for conditional approval of Canalevia for treatment of CID in dogs. Jaguar has now completed three of the four required technical sections—the CMC, Effectiveness, and Environmental Impact technical sections—of the Company's application for conditional approval of Canalevia for CID in dogs. We anticipate filing the Target Animal Safety technical section with CVM in the second quarter of 2019. If Canalevia is approved for CID in dogs, we expect to conduct the commercial launch of Canalevia for this indication in 2020.

Crofelemer is extracted from the Croton lechleri tree, which we sustainably harvest and manage through programs that we have been developing over the past 29 years. This process has involved working with communities to plant trees, obtaining permits for export, and creating a supply network that is robust and reliable.

We continue to have working relationships with partners that began in the 1990s. Additionally, through the establishment of a nonprofit called the Healing Forest Conservancy (HFC), our team has created a long term mechanism for benefit sharing that recognizes the intellectual contribution of indigenous populations. This program is intended to contribute to the continued strength and effectiveness of the valued and strategically important relationships we have carefully cultivated over the past 29 years.

Product Pipeline

In addition to our Mytesi (crofelemer) product that is approved by the U.S. FDA for the symptomatic relief of noninfectious diarrhea in adults with HIV/AIDS on antiretroviral therapy, we are also developing a pipeline of prescription drug product candidates to address unmet needs in gastrointestinal health through Napo. Mytesi (crofelemer) is a novel, first in class anti secretory agent which has a basic normalizing effect locally on the gut, and this mechanism of action has the potential to benefit multiple disorders. Clinical trials demonstrated that nearly 80% of Mytesi users experienced an improvement in their diarrhea over a four week period. At week 20 of the pivotal trial, over half the patients had no watery stools, or a 100% decrease, and 83% had at least a 50% decrease in watery stools. Our Mytesi pipeline currently includes prescription drug product candidates for four follow on indications, several of which are backed by Phase 2 evidence from completed Phase 2 trials. In addition, a second generation proprietary anti secretory agent is in development for cholera.

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Napo Prescription Drug Product Candidates

Product Candidates	Indication	Completed Milestones	Current Phase of Development	Anticipated Near Term Milestones*
Mytesi	Cancer therapy related diarrhea (CTD)	•Two investigator initiated (IIT) clinical trials funded by Genentech Roche & Puma •Met with FDA in March 2019 to discuss the anticipated protocol for a planned pivotal trial	Phase 3	•Availability of interim data IIT for Genentech Roche-funded trial in Q2 2019
Mytesi	Supportive care for IBD	•Safety •Multiple Phase 2 studies completed in various secretory diarrhea (not IBD)	Phase 2	•Protocol development with KOLs for discussions with FDA
Formulation of crofelemer	Rare disease indications (SBS & CDD)	•Phase 1 study •Orphan drug designation for SBS	Phase 2	•Formulation/IIT, Abu Dhabi, Protocol design
Mytesi	Irritable bowel syndrome—diarrhea predominant (IBS D)	•Phase 1 study •Two Phase 2 studies completed	Phase 2	•Publication of supplemental analysis of Phase 2 data
Mytesi	Idiopathic/functional diarrhea	•Safety •Multiple Phase 2 studies completed in various secretory diarrhea •IIT request accepted	Phase 2	•Initiation of IIT
SB 300 (lechlemer)	Second generation anti secretory agent for multiple indications including cholera	•Animal and human studies in secretory diarrhea; successful cholera trial design for anti secretory mechanism of action with API	Pre IND	•Formulation / POC

*Clinical trials are funding dependent

Estimated Size of Mytesi Target Markets

We believe the medical need for Mytesi is significant, compelling, and unmet, and that doctors are looking for a drug product with a mechanism of action that is distinct from the options currently available to resolve diarrhea. A growing percentage of HIV patients have lived with the virus in their gut for 10+ years, often causing gut enteropathy

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and chronic or chronic episodic diarrhea. According to data from the U.S. Centers for Disease Control and Prevention, by 2020 more than 70% of Americans with HIV are expected to be 50 and older.(1)

Market	Number of Competitors for Mytesi's Approved/ Anticipated Labelled Indication	Market Size/Potential
HIV D	0	We estimate the U.S. market revenue potential for Mytesi to be approximately $100 million in gross annual sales
CTD	0	An estimated 650,000 U.S. cancer patients receive chemotherapy in an outpatient oncology clinic.(2) Comparable supportive care (i.e. CINV) product sales of ~$620 million in 2013, which is projected to reach $1.0 billion by 2020(3)
IBD	0	Estimated 1,171,000 Americans have IBD(4)
IBS D	3	Most IBS products have estimated revenue potential of greater than $1.0 billion(5)
CDD/SBS Cholera (hydration maintenance)	0	Financial benefits of Orphan drug Designation
PRV (SB 3000)	0	In recent transactions by other companies, priority review vouchers have sold for $67 million to $350 million(6)

(1) HIV Among People Aged 50 and Older (https://www.cdc.gov/hiv/group/age/olderamericans/index.html)

(2) Centers for Disease Control and Prevention. Preventing Infections in Cancer Patients: Information for Health Care Providers (cdc.gov/cancer/preventinfections/providers.htm)

(3) Heron Therapeutics, Inc. Form 10 K for the fiscal year ended December 31, 2016

(4) 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

(5) Merrill Lynch forecasts peak US sales of roughly $1.5 bn for Ironwood's Linzess (http://247wallst.com/healthcare business/2015/04/27/key-analyst-sees-nearly-30-upside-in-ironwood); Rodman & Rensha annual sales of Synergy Pharmaceuticals' Trulance at $2.3 bn in 2021 (Source: https://www.benzinga.com/analyst-ratings/analyst-color/17/03/9224181/analyst-synergy-pharma-could-achieve-su

(6) In Aug. 2015, AbbVie Inc. bought a priority review voucher from United Therapeutics Corp for $350 million (http://www.reuters.com/article/us-abbvie-priorityreview/abbvie-buys-special-review-voucher-for-350-million-idUSKCN0 In July 2014, BioMarin announced that it had sold a priority review voucher to Sanofi and Regeneron for $67.5 million. (https://investors.biomarin.com/2014-07-30-BioMarin-Sells-Priority-Review-Voucher-for-67-5-Million).

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The following diagram illustrates the mechanism of action of our human and animal gastrointestinal drug products and drug product candidates, which normalize chloride and water flow and transit time of fluids within the intestinal lumen.

Business Strategy

Our goal is to become a leading pharmaceutical company with first in class, sustainably derived products that address significant unmet gastrointestinal medical needs globally. To accomplish this goal, we plan to:

Expand Mytesi by leveraging our significant gastrointestinal knowledge, experience and intellectual property portfolio

Mytesi is a novel, first in class anti secretory agent which has a basic normalizing effect locally on the gut, and this mechanism of action has the potential to benefit multiple gastrointestinal disorders. 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. Jaguar, through Napo, holds extensive global rights for Mytesi. Mytesi is in development for multiple possible follow on indications, including diarrhea related to targeted cancer therapy; orphan drug indications for infants and children with congenital diarrheal disorders and short bowel syndrome; supportive care for inflammatory bowel disease; irritable bowel syndrome; and for idiopathic/functional diarrhea. In addition, a second generation proprietary anti secretory agent is in development for cholera.

Our management team collectively has more than 100 years of experience in the development of gastrointestinal prescription drug and non prescription products. This experience covers all aspects of product development, including discovery, preclinical and clinical development, GMP manufacturing, and regulatory strategy. Key members of this team successfully developed Mytesi.

Establish and expand commercial capabilities in Mytesi sales and marketing efforts

As announced on August 7, 2017, we appointed Pete Riojas, a 29 year pharmaceutical industry veteran, to lead Napo's direct sales organization, which is comprised of Mytesi field sales representatives strategically positioned to cover U.S. geographies with the highest potential. Additionally, in June 2018, we hired Robert J. Griffing, a seasoned industry veteran with a broad range of experience that includes commercializing supportive care and HIV treatments, as chief commercial officer for Napo. With support provided by concomitant marketing, promotional activities, patient empowerment programs, including an integrated social digital campaign, and medical education initiatives described below, we expect a proportional response in the number of patients treated with Mytesi.

In June 2018, as stated above, Napo entered into an agreement with RedHill Biopharma, a specialty biopharmaceutical company primarily focused on late clinical stage development and commercialization of proprietary drugs for gastrointestinal diseases and cancer, to establish a U.S. co promotion program for Mytesi. RedHill's specialized, GI focused field sales force promotes Mytesi to health care practitioners in 36 U.S. territories that contain

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significant numbers of HIV patients and health care practitioners that are not currently covered by Napo's field sales force. In these regions, RedHill sales representatives target gastroenterologists who see large populations of people living with HIV, along with nurse practitioners and physician assistants. RedHill field representatives also target lower level ART prescribing infectious disease specialists in regions currently covered by Napo's sales force. Four RedHill inside sales representatives actively target health care practitioners in other regions not covered by the Napo or RedHill field representatives. We believe this co promotion program will play a significant role in extending the reach of our commercial efforts into the GI medical community in support of the treatment of people living with HIV (PLWH) with Mytesi. Under the terms of the Agreement, RedHill is compensated based on performance, and the program can be extended by agreement between the two companies , as it was in January 2019.

Leverage our relationships with key opinion leaders regarding development of follow on indications

To date, more than 30 key opinion leaders (KOLs) who are recognized specialists in HIV patient care, CTD, IBD, IBS, cholera, SBS, CDD and equine gut health, are participating in our scientific advisory board or KOL advisory program in some manner.

Establish partnerships to support moving pipeline indications to pivotal clinical trials

Jaguar is actively pursuing development of a robust pipeline of potential follow on indications for crofelemer, and the Company's goal is to establish partnerships to support moving pipeline indications to pivotal clinical trials.

Strategically sequence the development of follow on indications of Mytesi and seek geographically focused licensing opportunities

As announced September 24, 2018, Jaguar and Knight Therapeutics Inc. ("Knight") entered into a Distribution, License and Supply Agreement that grants Knight the exclusive right to commercialize Mytesi and related products in Canada and Israel.

Although it is possible that we may enter into additional corporate partnering relationships related to Mytesi, our intention would be to retain all commercialization and promotional rights in the U.S., so that we do not become primarily a royalty collecting organization, and we are opposed to entering into any Mytesi partnering relationship that would require splitting indications. We are seeking to put limited geographically focused partnerships in place in the near term, while also considering possibilities for a worldwide partnership with a leading global entity (excluding the US exclusive commercial rights) in the field of gastrointestinal care and cancer in the long term.

Reduce risks relating to product development

Risk reduction is a key focus of our product development planning. Mytesi is approved for chronic indication, providing us the ability to leverage this corresponding safety data when seeking approval for planned follow on indications that are also chronic or chronic episodic indications. Crofelemer manufacturing is being conducted at two FDA-inspected and approved locations, including a new, multimillion dollar commercial manufacturing facility. In an effort to reduce risk further, we have implemented the following approach: First, we meet with key opinion leaders, typically at medical conferences—as we did in 2017 at Digestive Disease Week for IBS and IBD, the American Society of Clinical Oncology annual meeting, and the Multinational Association of Supportive Care and Congress. Next, we confirm unmet medical needs with these key opinion leaders and discuss the practicality of patient enrollment and trial implementation. We then generate protocols to discuss with the FDA, seeking, when possible, special protocol assessments. Our goal, by the time we start devoting significant funds to a clinical trial, is to have de risked the program as much as we believe we possibly can, in particular the regulatory pathway. We believe this approach will lead to better long term outcomes for our products in development.

We believe that Jaguar is poised to realize a number of synergistic, value adding benefits—and an expanded pipeline of important human follow on indications and a second generation anti secretory agent, upon which to build global partnerships.

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In May 2016, the New Drug Application ("NDA") and commercial rights for human applications of crofelemer (Mytesi) previously licensed to Salix Pharmaceuticals, Inc. ("Salix") were transferred to Napo. The active pharmaceutical ingredient ("API") in Mytesi is crofelemer, our proprietary, patented gastrointestinal anti secretory agent sustainably harvested from the rainforest.

Diarrhea is a common adverse event seen with chemotherapy agents typically used in breast and colon cancers, and in particular in the more recently introduced therapeutic classes of epidermal growth factor receptor ("EGFR") monoclonal antibodies and tyrosine kinase inhibitors ("TKI") often used for chronic adjuvant care management of cancer. The increased need for and use of these agents has made diarrhea one of the most disabling issues for cancer patients.

We will seek partnerships outside the United States for the above indications, while focusing on development, and commercial access in the United States directly. We are also focused on investigating SB 300 (lechlemer) for various gastrointestinal indications. Lechlemer is a proprietary Jaguar pharmaceutical product, a standardized botanical extract distinct from crofelemer, also sustainably derived from the Croton lechleri tree.

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. Additionally, we believe lechlemer represents a long term pipeline opportunity as a second generation anti secretory agent, on a global basis, for multiple gastrointestinal diseases—especially in resource constrained countries where cost of goods is a factor, in part, because requirements often exist in such regions for drug prices to decrease annually.

The Company has presented Phase 2 data on crofelemer for the treatment of devastating dehydration in cholera patients from the renowned International Centre for Diarrhoeal Disease Research (icddr,b) in Bangladesh, and Napo plans to follow the same study design for a trial conducted in association with icddr,b in support of development of lechlemer for the potential cholera related indication.

Our portfolio development strategy is based on identifying indications that are potentially high value because they address important medical needs that are significantly or globally unmet, and then strategically sequencing indication development priorities, second generation product pipeline development, and partnering goals on a global basis.

Our technology for proprietary gastrointestinal disease products is central to the product pipelines of both veterinary and human indications. Crofelemer is also the API in Canalevia, our lead prescription drug product candidate, intended for the treatment of chemotherapy induced diarrhea in dogs. We expect our first veterinary prescription product launch will be Canalevia for chemotherapy induced diarrhea, an interesting commercial synergy with the pursuit of follow on indications for Mytesi.

Mytesi Clinical Data

Mytesi has been clinically demonstrated to have:

- Minimal absorption, with plasma concentrations below the level of detection
- No clinically relevant drug drug interactions
- No effect on viral load or CD4 counts
- Adverse events comparable to those with placebo

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The efficacy of Mytesi 125 mg delayed release tablets twice daily was evaluated in a randomized, double blind, 24 week, multicenter study (the ADVENT trial) comprised of a placebo controlled (1 month) treatment period and a placebo free (5 month) treatment period. The study enrolled HIV positive patients on stable ART with a history of diarrhea for 1 month or more. In the Mytesi 125mg bid group, more than twice as many patients (18% vs. 8% on placebo, $p<0.01$) achieved the highly rigorous endpoint defined as reduction to ≤2 watery stools per week for 2 out of the 4 weeks in the placebo controlled period (the average baseline in the ADVENT population was 20 watery stools per week).

In a supplemental analysis of the ADVENT study population, 78% of patients in the Mytesi 125mg BID group experienced a decrease in watery stools at week 4. Among these patients that experienced a decrease, 61% had at least a 50% decrease in watery stools. At week 20, 89% of patients in the Mytesi BID group experienced a decrease in watery stools. Among these patients that experienced a decrease, 83% had at least a 50% decrease in watery stools, and over half of patients had no watery stools at all (100% decrease).

Products in Development

Cancer Therapy Related Diarrhea (CTD)

Diarrhea related to TCT is a common problem with a relevant mechanism for crofelemer

National Cancer Institute Criteria for Grading Severity of Diarrhea

	Grade 1	Grade 2	Grade 3	Grade 4
Patients without a colostomy	Increase of <4 stools per day over pretreatment	Increase of 4 to 6 stools per day or nocturnal stools	Increase of ≥7 stools per day or incontinence; need for parenteral support for hydration	Physiologic consequences requiring intensive care; hemodynamic collapse

Diarrhea is a common adverse event seen with chemotherapy agents in the therapeutic classes of epidermal growth factor receptor (“EGFR”) tyrosine kinase inhibitors (“TKI’s”) and EGFR monoclonal antibodies (for breast, lung, and other malignancies). The increased need for and use of these agents has made diarrhea one of the most disabling issues for cancer patients. Crofelemer offers the potential for an appropriate mechanism of action against this likely secretory diarrhea and has prompted interest among physicians concerned about this diarrheal symptom, stimulating the aforementioned investigator initiated trials. Diarrhea is also a common adverse event seen with chemotherapy agents used in colorectal and gastric cancers, and chronic maintenance chemotherapy. There are currently no anti diarrhea agents approved generally for chemotherapy induced diarrhea.

Clinical Studies

A study titled 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 is currently underway in conjunction with Georgetown University. The primary objective of the study is to characterize the incidence and severity of diarrhea in patients receiving investigational therapy in the setting of prophylactic anti diarrheal management.

A second study, titled An open label study to characterize the incidence and severity of diarrhea in patients with early stage HER2+ breast cancer treated with adjuvant trastuzumab and neratinib followed by neratinib monotherapy, and intensive anti diarrhea prophylaxis, is currently underway in conjunction with the University of California at San Francisco. The study is designed to evaluate crofelemer as a salvage anti diarrheal therapy used with the investigational breast cancer agent neratinib. The primary objective is to characterize the incidence and severity of diarrhea in patients with early stage breast cancer receiving adjuvant trastuzumab and neratinib followed by 1 year of

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neratinib monotherapy in the setting of prophylactic anti diarrheal management. The secondary objectives are to evaluate the activity of crofelemer as a rescue anti diarrheal medication; to assess neratinib adherence, holds, delays, and early discontinuation throughout the course of study therapy, which includes patients receiving neratinib for >1 year; and to assess overall toxicity including constipation and cardiac toxicity with concomitant neratinib and trastuzumab.

Irritable Bowel Syndrome—Diarrhea Predominant (IBS D)

Diarrhea is a common symptom of irritable bowel syndrome (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. According to the U.S. FDA, studies estimate that IBS affects 10 to 15 percent of adults in the United States.

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 come on the market, 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.

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.

The largest group of IBS sufferers are those with the subtype referred to as IBS M (mixed diarrhea and constipation). IBS M is also referred to as IBS A, because the condition often involves frequent alternating between IBS D and IBS C (constipation predominant). IBS M is distressing for patients as well as difficult to diagnose and manage, and is often associated with pain and urgency as well as significant abdominal distension and bloating. No approved drugs currently exist for IBS M. Leading gastroenterologists have stated that IBS C drugs may cause diarrhea in an IBS M patient, and an IBS D drug may cause significant constipation. Since Mytesi has not caused constipation in clinical trials or real-world experience, we therefore believe an opportunity exists for an IBS M indication for Mytesi. Resultingly, and due to the demonstrated safety of Mytesi for chronic use and its demonstrated benefit for abdominal pain in women, Napo is considering expanding development efforts to evaluate the IBS M indication.

Clinical Study

Crofelemer has been tested in safety studies and two significant Phase 2 studies for d-IBS (diarrhea-predominate Irritable Bowel Syndrome) as detailed below.

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Completed Studies—IBS D

Phase 2a—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.

n=245 subjects

61 placebo

62 125 mg crofelemer BID

59 250 mg crofelemer BID

62 500 mg crofelemer BID

IBS symptoms (pain, urgency, stool frequency and consistency, and adequate relief) were self reported by the patients via an interactive voice response system. Patients needed to exhibit active disease during the two week baseline period as defined by a mean daily stool frequency greater than or equal to 2/day, pain score greater than or equal to 1 and stool consistency greater than or equal to 3 (5 point Lickert scale for pain and consistency) to be enrolled. Patients received treatment for 12 weeks followed by a two week treatment free period.

The protocol specified primary efficacy measure was daily stool consistency. Statistical analysis of the primary endpoint found no significant differences between placebo and any of the crofelemer dose groups ($p \geq 0.1434$) and no significant dose relationship was seen with regard to change from Baseline to Month 3 in stool consistency scores ($p = 0.1165$) in the ITT population.

A supplementary analysis of Rome Foundation defined stool consistency and abdominal pain showed positive results. Responders were subjects who had stool consistency score of ≥ 4 for < 25% of days in a given week and ≥ 30% improvement in abdominal pain scores a given week (i.e., Rome Foundation defined stool consistency and abdominal pain responders).

When we look at a supplemental analysis at a reduction in a composite abdominal pain/stool consistency endpoint, the regulatory endpoint in accordance with FDA guidance, we see at the 125 mg dose bid a significant 15% difference with just women patients compared to placebo; and a significant 11% when we include both men and women. The current IBS-d products on the market have a 7 8% reduction (Viberzi and Xifaxan).

In this analysis, Rome Foundation defined stool consistency and abdominal pain responders were significantly more likely during the entire 3 months in the 125 mg BID group when compared with placebo (24.2% versus 13.1%, $p = 0.0399$) and there was a statistical trend in favor of crofelemer 125 mg BID during Months 1 through 2 (27.4% versus 16.4%, $p = 0.0640$). Similar positive effects of crofelemer 125 mg BID were observed in female subjects ($n = 183$). When the supplementary analysis was applied to the female patients, crofelemer at a dose of 125 mg BID was superior to placebo at Month 3 (26.1% vs 10.9%, $p=0.0337$).

- Results: The 125mg bid of crofelemer exhibited a consistent response during each month among most efficacy endpoints in women with d IBS reaching statistical significance ($p<0.05$) for pain.
- Crofelemer had little effect on the stool consistency score, though there was a trend toward reduced stool frequency.
- Treatment benefits were not apparent in men, although relatively few men enrolled in the trial (13 16/group).

As with previous trials of crofelemer, no drug related serious adverse events were reported. Adverse event rates were similar across all dose groups, although in the two highest doses (250 and 500 mg bid) there were a higher percentage of dropouts. There were no drug related or dose related differences in constipation. During the two week treatment free follow up period symptoms approached baseline levels.

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Safety: Crofelemer at doses of 125, 250 and 500 mg had a safety profile that was generally similar to placebo among men and women with IBS-D.

Phase 2—A Randomized, double blind, placebo controlled study to assess the safety and efficacy of crofelemer for the symptomatic treatment of diarrhea predominant irritable bowel syndrome (d IBS) in 240 female subjects 18 years or older with active d IBS according to the Rome II criteria for the diagnosis of d IBS.

The study consisted of a 2 week screening period and a 12 week blinded treatment period followed by a 4 week treatment free follow up period. During the 12 week treatment period 240 subjects were given 125 mg of crofelemer BID or placebo BID and recorded daily assessments of their IBS symptoms in the interactive voice response system.

The primary endpoint was the change from baseline for overall percentage of abdominal pain/discomfort free days (PFDs). On a daily basis, respondents recorded the intensity of their abdominal pain/discomfort for that day using the 5 pint Likert scale: 0=none, 1=mild, 2=moderate, 3=intense, 4=severe. Any day that a score of zero (0) was recorded was considered a PFD.

Stool consistency and abdominal pain endpoints were analyzed using definitions of symptom improvement from a recent FDA guidance on IBS endpoints (March 2010) and recommendations of the Rome Foundation (letter dated 28 June 2010) concerning the IBS endpoints described in this guidance.

Results: The overall increase in pain free days (protocol specified primary endpoint) for subjects in the crofelemer group was not statistically significant when compared with subjects in the placebo group ($p = 0.5107$)

A supplementary analysis of abdominal pain showed positive results. Responders were subjects who had ≥ 30% improvement in abdominal pain scores a given week (i.e., FDA defined abdominal pain responders; this definition of abdominal pain responders was presented in the March 2010 guidance on IBS endpoints).

In this analysis, abdominal pain responders were significantly more likely during Months 1 through 2 (58.3% versus 45.0%, $p = 0.0303$) and during the entire 3 months (54.2% versus 42.5%, $p = 0.0371$) in the crofelemer group when compared to placebo.

Safety: The overall safety profile for crofelemer 125 mg BID for 12 weeks was comparable to that observed with placebo and was consistent with the IBS population under study.

Rare Pediatric Disease Indications: Congenital Diarrheal Disorders and Short Bowel Syndrome (SBS)

Congenital diarrheal disorders (CDD) are a group of rare, chronic intestinal channel diseases, occurring 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 much more prevalent in regions where consanguineous marriage 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 immediate therapy to prevent death and limit lifelong disability.

Potential Orphan Drug: Congenital Diarrheal Disorders (CDD) & Short Bowel Syndrome (SBS)

Clinical Study—CDD

We have completed safety studies of crofelemer in children as young as 3 months of age, and Napo has accepted a request for support submitted by Dr. Mohamad Miqdady, Chief of Pediatric Gastroenterology, Hepatology and

Nutrition at Sheikh Khalifa Medical City (SKMC) in Abu Dhabi, for an investigator initiated trial of crofelemer, the active pharmaceutical ingredient in Mytesi, for CDD in children.

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A pre clinical study in mice, conducted by an independent third party investigator, is underway to support possible orphan drug designation for crofelemer for Congenital Diarrheal Disorders (CDD). This animal model study is examining the effects of crofelemer on diarrhea caused by microvillous inclusion disease (MVID), a very rare autosomal recessive disorder which belongs to the CDD category.

SBS is a complex condition characterized by malabsorption of fluids and nutrients due to congenital deficiencies or surgical resection of small bowel segments. Consequently, patients suffer from symptoms such as debilitating diarrhea, malnutrition, dehydration and imbalances of fluids and salts. This could be due to either a genetic disorder or premature birth. In countries such as the United Arab Emirates and Saudi Arabia, SBS occurs with much higher incidence. Napo recently visited with medical centers in this region.

We have received orphan drug status for Mytesi (crofelemer) for the SBS pediatric indication and are pursuing orphan drug status for CDD. The mission of the FDA Office of Orphan Products Development 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.

IBD—Supportive Care:

Key opinion leaders (“KOLs”) identified an unmet need to treat diarrhea in IBD patients, particularly in specific subsets of patients. KOLs felt all IBD patients who undergo ileal pouch anal anastomosis (IPAA) surgery suffer 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 may 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, KOLs felt crofelemer’s novel mechanism of action may 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. Secretory diarrhea occurs when the intestine does not complete absorption of electrolytes and water from luminal contents. This can happen when a nonabsorbable, osmotically active substance is ingested (“osmotic diarrhea”) or when electrolyte absorption is impaired (“secretory diarrhea”).

Secretory diarrhea can result from bacterial toxins, luminal secretagogues (such as bile acids or laxatives), reduced absorptive surface area caused by disease or resection, circulating secretagogues (such as various hormones, drugs, and poisons), and medical problems that compromise regulation of intestinal function. These studies in acute diarrhea support the normalizing aspect of the mechanism of action, regardless of the cause of the diarrhea, and are supportive of the supportive care indication under development in IBD patients.

Clinical Study

Mytesi has safety studies that support chronic use for the current approved indication, and has demonstrated statistically significant results in multiple supportive care settings, though not specifically in IBD patients. Next steps would include a Phase 2 proof of concept study for supportive care in patients with IBD.

Completed Study—Travelers’ Diarrhea (supportive care)

Phase 2—A study of crofelemer in 184 persons in a double blind, placebo controlled study for the symptomatic treatment of acute diarrhea among travelers to Jamaica and Mexico.

The study was designed to evaluate the effectiveness of crofelemer in the treatment of travelers' diarrhea.

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A total of 184 persons from the United States who acquired diarrhea in Jamaica or Mexico were enrolled in a double blind, placebo controlle