

Jaguar Health, Inc.  
Form 10-K  
April 09, 2018

Use these links to rapidly review the document

[TABLE OF CONTENTS](#)

[ITEM 8. FINANCIAL STATEMENTS AND SUPPLEMENTARY DATA](#)

[Table of Contents](#)

**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, 2017

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**  
(State or other jurisdiction of  
incorporation or organization)

**46-2956775**  
(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**  
Common Stock, Par Value \$0.0001 Per Share

**Name of each exchange on which registered**  
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

## Edgar Filing: Jaguar Health, Inc. - Form 10-K

Indicate by check mark whether the registrant has submitted electronically and posted on its corporate Web site, if any, every Interactive Data File required to be submitted and posted 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 and post 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 <input type="checkbox"/>	Accelerated filer <input type="checkbox"/>	Non-accelerated filer <input type="checkbox"/> (Do not check if a smaller reporting company)	Smaller reporting company <input checked="" type="checkbox"/>
			Emerging growth company <input checked="" type="checkbox"/>

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, 2017, the aggregate market value of the registrant's common stock held by non-affiliates was approximately \$6,574,176 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 9, 2018 was 168,316,084, consisting of 125,698,191 shares of voting common stock and 42,617,893 shares of non-voting common stock. The company also had 5,524,926 shares of convertible preferred stock outstanding.

### DOCUMENTS INCORPORATED BY REFERENCE

Portions of the proxy statement for the registrant's 2018 Annual Meeting of Stockholders, or Proxy Statement, to be filed within 120 days of the end of the fiscal year ended December 31, 2017 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.

---

Table of Contents**TABLE OF CONTENTS**

<b>Item No.</b>		<b>Page No.</b>
<b><u>PART I</u></b>		
<u>Item 1.</u>	<u>Business</u>	<u>1</u>
<u>Item 1A.</u>	<u>Risk Factors</u>	<u>42</u>
<u>Item 1B.</u>	<u>Unresolved Staff Comments</u>	<u>76</u>
<u>Item 2.</u>	<u>Properties</u>	<u>76</u>
<u>Item 3.</u>	<u>Legal Proceedings</u>	<u>76</u>
<u>Item 4.</u>	<u>Mine Safety Disclosure</u>	<u>77</u>
<b><u>PART II</u></b>		
<u>Item 5.</u>	<u>Market for Registrant's Common Equity, Related Stockholder Matters and Issuer Purchases of Equity Securities</u>	<u>78</u>
<u>Item 6.</u>	<u>Selected Financial Data</u>	<u>79</u>
<u>Item 7.</u>	<u>Management's Discussion and Analysis of Financial Condition and Results of Operation</u>	<u>80</u>
<u>Item 7A.</u>	<u>Qualitative and Quantitative Disclosures About Market Risk</u>	<u>110</u>
<u>Item 8.</u>	<u>Financial Statements and Supplementary Data</u>	<u>111</u>
<u>Item 9.</u>	<u>Changes in and Disagreements with Accountants on Accounting and Financial Disclosure</u>	<u>162</u>
<u>Item 9A.</u>	<u>Controls and Procedures</u>	<u>162</u>
<u>Item 9B.</u>	<u>Other Information</u>	<u>163</u>
<b><u>PART III</u></b>		
<u>Item 10.</u>	<u>Directors, Executive Officers and Corporate Governance</u>	<u>164</u>
<u>Item 11.</u>	<u>Executive Compensation</u>	<u>164</u>
<u>Item 12.</u>	<u>Security Ownership of Certain Beneficial Owners and Management and Related Stockholder Matters</u>	<u>164</u>
<u>Item 13.</u>	<u>Certain Relationships and Related Transactions, and Director Independence</u>	<u>164</u>
<u>Item 14.</u>	<u>Principal Accountant Fees and Services</u>	<u>164</u>
<b><u>PART IV</u></b>		
<u>Item 15.</u>	<u>Exhibits, Financial Statement Schedules</u>	<u>165</u>
<b><u>SIGNATURES</u></b>		<u>175</u>

Table of Contents

**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" or the negative 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. In

Table of Contents

the field of animal health, we are focused on developing and commercializing first-in-class gastrointestinal products for companion and production animals, foals, and high value horses.

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 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.

With the merger effective, we believe that our newly combined company is poised to realize a number of synergistic, value adding benefits and an expanded pipeline of potential blockbuster human follow-on indications, a second-generation anti-secretory agent, as well as a pipeline of important animal indications for crofelemer, upon which to build global partnerships. As previously announced, Jaguar, through Napo, now controls commercial rights for Mytesi for all indications, territories and patient populations globally, and crofelemer manufacturing is being conducted at a new, multimillion-dollar commercial manufacturing facility that has been FDA-inspected and approved. Additionally, several of the drug product candidates in Jaguar's Mytesi pipeline are backed by strong Phase 2 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 cancer therapy-related diarrhea; 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 as a second-generation anti-secretory agent for use in cholera patients. Mytesi has received orphan-drug designation for SBS.

Napo launched Mytesi in early 2017 with one full-time-equivalent Mytesi sales representative focused on targeting high-decile prescribing HIV doctors. Napo significantly expanded its internal national salesforce for Mytesi in Q4, 2017 through the hire in key U.S. markets of six additional full-time sales representatives experienced in the sale of drugs to HIV physicians and gastroenterologists. Today our sales force of ten highly trained sales representatives, a regional sales director, and our national sales manager are now fully on board and trained on Mytesi. Seven of these sales representatives are former long-term employees of the HIV portfolio business of drugmaker Bristol-Myers Squibb, while the remainder of the team possess extensive experience in drug sales to both HIV healthcare providers and gastroenterologists. With support provided by concomitant marketing, promotional activities, patient empowerment programs and medical education initiatives described below, we expect a proportional response 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 percent of respondents living with HIV/AIDS reported that they currently have diarrhea, while 56 percent 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 percent of U.S. gastroenterologists see patients with HIV/AIDS in their practice.

Key to the success of our sales representatives in growing Mytesi 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 3,500 high volume ART prescribing HIV specialists, and

Table of Contents

the 1,500 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 Miami/South Florida, Los Angeles/Palm Springs, New York, Houston, Chicago/St. Louis, Indianapolis, Kansas City, Alabama, Atlanta, San Francisco, DC, Pennsylvania, New Jersey, Delaware, Maryland, Mississippi and Louisiana.

As we announced on January 22, 2018, preliminary sales of Mytesi for the period of August 1, 2017 through December 31, 2017 the period following the close of the merger were approximately \$1.40 million, and, as we announced March 2, 2018, we anticipate that Mytesi gross sales for the period of January 1, 2017 through March 31, 2018 will total approximately \$3.2 million. Jaguar estimates the potential U.S. market for Mytesi to be approximately \$100 million in gross annual sales.

From September 1, 2017 through November 30, 2017, there was an increase of 86% in new Mytesi prescribers among gastroenterologists and 8% in HIV specialists, coincident with the deployment of our direct sales force. According to data provided by IQVIA, the number of Mytesi prescriptions written by physicians increased an average of 9.5% each month over the prior month during the August 1, 2017 through December 31, 2017 period. Additionally, patient redemptions of our Mytesi Copay Savings Card increased an average of 7% each month over the prior month during the same period.

As announced January 22, 2018, Napo recently completed the training of 29 health care practitioners (HCPs) and ten patient advocates to serve as members of the Napo Speakers Bureau. Medical education presentations led by participating HCPs a group that includes HIV/AIDS specialists, infectious disease specialists, gastroenterologists, colorectal surgeons, and nurse practitioners will 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 will provide information to people living with HIV (PLWH) about the prevalence of diarrhea in PLWH and offer guidance about talking to HCPs regarding diarrhea-related concerns.

As part of Napo's medical and patient education program, the Mytesi direct sales force are planning more than 1,400 live and virtual educational events for 2018. Live events will largely take place in the following key geographies covered by the Mytesi sales team: Miami/South Florida, Los Angeles/Palm Springs, New York, Houston, Chicago/St. Louis, Indianapolis, Kansas City, Alabama, Atlanta, San Francisco, DC, Pennsylvania, New Jersey, Delaware, Maryland, Mississippi and Louisiana.

As we announced March 2, 2018, Napo has signed an agreement with pharmacy services provider Transition Patient Services (TPS) to help streamline and expand nationwide patient access to Mytesi. Headquartered in Trevoze, Pennsylvania, TPS is a direct-to-patient hub-service pharmacy licensed in all 50 states and dedicated to simplifying medication access, increasing patient engagement, reducing prescription abandonment, and enhancing patient outcomes through confirmed medication acquisition and improved adherence. Under the terms of the agreement, TPS will operate a nationwide pilot program for Mytesi, expected to begin in March 2018. The core benefits of the program, named Mytesi Direct, include streamlining prescription fulfillment for Mytesi in order to ensure that Mytesi users receive their prescription quickly, coordinating with other Napo programs such as the Mytesi Copay Savings Card and the NapoCares Patient Assistance Program to help ensure that patient out-of-pocket expenses for Mytesi are as low as possible, and improving Mytesi refill adherence through the transmission of renewal reminders to patients. We expect the Mytesi Direct program to significantly reduce barriers to Mytesi access, acquisition and adherence in a highly patient-friendly and prescriber-friendly manner helping us expand the number of patients able to benefit from the novel, first-in-class anti-secretory mechanism of action of Mytesi.

New cfofelemer (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 Cfofelemer Use Gives Clinically Relevant Reductions in HIV-Related Diarrhea*. IAS features the latest HIV science, including basic, clinical and

## Edgar Filing: Jaguar Health, Inc. - Form 10-K

### Table of Contents

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 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 as 67 stools in a week).

In October 2017, Napo launched a national campaign called "Keep your pants on... Unless you don't want to" to highlight the need to recognize and treat diarrhea in people living with HIV/AIDS (PLWHA). The campaign ([keep-your-pants-on.com](http://keep-your-pants-on.com)), which launched initially to the 10,000 participants in the AIDS Walk Los Angeles event on October 15, 2017, is designed to raise awareness and to engage PLWHA in a fun and light way to discuss a topic that can be embarrassing. The campaign integrates live third-party events, including the Greater Palm Springs Pride event taking place in November 2017, with social media on the web, Twitter, and Facebook. Campaign participants are encouraged to use the hashtag #KeepYourPantsOn when posting photos and videos to social media. Napo is also running "Keep Your Pants On" digital ads on more than 25 HIV and LGBT media outlets around the U.S.

Additionally in Q4 2017, Napo launched a print and digital advertising campaign titled "Enough is Enough" to target PLWHA who are tired of planning their lives around diarrhea as well as HIV physicians and gastroenterologists. The campaign is centered around national HIV magazines, local HIV publications, and publications targeting physicians.

In October 2017, Napo established a scientific advisory board for each potential follow-on indication currently planned for Mytesi. Napo has developed relationships with more than 30 physicians, pharmacists and patient advocates around the world who are recognized specialists and key opinion leaders in the planned Mytesi follow-on indications, and is conducting outreach efforts to discuss the possibility of membership in Napo's new scientific advisory boards with these individuals. As announced on October 19, 2017, Dr. Lee Schwartzberg, MD, FACP, a nationally-recognized medical oncologist and hematologist, has joined Napo's scientific advisory board for cancer therapy-related diarrhea (CTD).

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, as a resource for media inquiries.

Napo's HIV Scientific Advisory Board will focus 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 is pursuing AIDS Drug Assistance Program (ADAP) formulary listing in states where Mytesi is not currently on ADAP formulary. This includes key states such as New York, Florida, California, Texas, and Georgia. The ADAP program provides Mytesi free of charge to patients who qualify and copay support for some patients who have insurance coverage.

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](http://mytesi.com/mytesi-savings.html).

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 demonstrating approval by the

## Edgar Filing: Jaguar Health, Inc. - Form 10-K

### Table of Contents

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.

Two investigator-initiated trials of Mytesi are underway in breast cancer patients suffering from CTD, one funded by Genetech Roche with Herceptin (enrolling patients), and one funded by Puma with neratinib (eurolling patients).

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.

In this era of novel targeted agents, epidermal growth factor receptor tyrosine kinase inhibitors (TKIs), in particular, may block natural chloride secretion regulation pathways in the normal gastrointestinal mucosa, thereby leading to secretory diarrhea. 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% in published studies. Diarrhea in this patient population has the potential to cause dehydration, potential infections, and 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, occurring exclusively 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 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 2018 to the 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 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 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



Table of Contents

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.

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.

Our management team has significant experience in gastrointestinal product development for both humans and animals. Napo was founded 28 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 28 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 132 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 85 pending patent applications worldwide in the human and animal 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. In addition, Mytesi is not systemically absorbed, so the classic approach of creating a generic drug by matching pharmacokinetic blood levels is not possible. A generic player would have to conduct costly and risky clinical trials.

The active ingredient in Mytesi is the basis for our eleven different animal health products across eight different species, all of which work by the same mechanism of action, which is highly conserved across all mammals. 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 animal health initiatives related to Canalevia, its drug product candidate for treatment of various types of diarrhea in dogs, and Equilevia, its non-prescription, personalized, premium product for total gut health in equine athletes.

As previously announced, Jaguar has received MUMS (Minor Use and Minor Species) designation status from the FDA for Canalevia for the indication of chemotherapy-induced diarrhea (CID) in dogs. Jaguar has completed clinical and manufacturing activity for Canalevia for this indication. 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 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 (crofelemer delayed-release tablets) for treatment of CID in dogs, based on CVM's review of the results of Jaguar's completed pilot

Table of Contents

study (CANA-001) of Canalevia for this indication. Jaguar has now completed two of the four required technical sections of the Company's application for conditional approval of Canalevia for CID in dogs.

As announced in December 2017, Jaguar has entered into a collaboration agreement with Seed Mena Businessmen Services LLC (SEED) for Equilevia. Based in Dubai in the UAE, SEED is affiliated with Seed Group, a diversified group of companies under the umbrella of The Private Office of His Royal Highness Sheikh Saeed Bin Ahmed Al Maktoum establishing strategic partnerships with multinational companies from around the globe in an aim to leverage Seed Group's network to support potential business expansion in the MENA (Middle East and North Africa) region. The UAE has become a global leader in horse racing, equine endurance competitions, and other equine athletic activities. Gut health is of critical importance in competitive horses, as conditions such as ulcers can meaningfully impair equine athlete performance, and colic can lead to the death of an otherwise healthy horse in a matter of hours. According to a third-party study titled *Results of a large-scale necroscopic study of equine colonic ulcers*, published in the Journal of Equine Veterinary Science in 2005, as many as 55% of performance horses have both colonic and gastric ulcers, and 97% of performance horses have either a gastric (87%) or a colonic (63%) ulcer.

Net sales in 2017 for Jaguar's non-prescription Neonorm Foal and Neonorm Calf products totaled approximately \$422,000. Collaboration revenue totaled approximately \$2.9M. Jaguar continues to maintain a relationship with the Company's dairy market distributor in addition to selling Neonorm directly to end users through neonorm.com.

We will consider additional animal formulations and additional animal product expenditures from time to time as part of portfolio planning and prioritization in the context of the combined company.

Crofelemer is extracted from the *Croton lechleri* tree, which we sustainably harvest and manage through programs that we have been developing over the past 28 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 28 years.

**Product Pipeline**

*Human Health*

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 percent 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. Initiation on a new antiretroviral therapy has been shown to cause diarrhea 15% of the time. Our Mytesi pipeline currently includes prescription drug product candidates for four follow-on indications, several of which are backed by strong Phase 2 evidence from completed Phase 2 trials. In addition, a second-generation proprietary anti-secretory agent is in development for cholera.

Table of Contents**Napo Prescription Drug Product Candidates**

<b>Product Candidates</b>	<b>Indication</b>	<b>Completed Milestones</b>	<b>Current Phase of Development</b>	<b>Anticipated Near-Term Milestones</b>
Mytesi	Cancer therapy-related diarrhea (CTD)	Two investigator-initiated clinical trials funded by Genentech, Roche & Puma	Phase 2	Protocol development with KOLs for discussions with FDA
Mytesi	Supportive care for IBD	Safety	Phase 2	Protocol development for discussions with FDA
		Multiple Phase 2 studies completed in various secretory diarrheas (not IBD)		
Formulation of crofelemer	Rare disease indications (SBS & CDD)	Phase 1 study	Phase 2	Formulation/IIT, Abu Dhabi
		Orphan designation for SBS		Pursue orphan-drug status for CDD
Formulation of crofelemer	Irritable Bowel Syndrome diarrhea predominant (IBS-D)	Phase 1 study	Phase 2	Protocol development with KOLs for discussions with FDA
		Two Phase 2 studies completed		P u b l i c a t i o n o f supplemental analysis of Phase 2 data
SB-300	Second-generation anti-secretory agent for multiple indications including cholera	Animal and human studies in secretory diarrheas; successful cholera trial design for anti-secretory mechanism of action with crofelemer	Pre IND	CMC development for SB-300  Pre-clinical and Phase 1 in 2018*

\*  

---

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 and chronic or chronic-episodic diarrhea. According to data from

## Edgar Filing: Jaguar Health, Inc. - Form 10-K

### Table of Contents

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.

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. <sup>(1)</sup> Comparable supportive care (i.e. CINV) product sales of ~\$620 million in 2013, which is projected to reach \$1.0 billion by 2020 <sup>(2)</sup>
IBD	0	Estimated 1,171,000 Americans have IBD <sup>(3)</sup>
IBS-D	3	Most IBS products have estimated revenue potential of greater than \$1.0 billion <sup>(4)</sup>
CDD/SBS-Orphan	0	Financial benefits of Orphan Designation
Cholera (hydration maintenance) PRV (SB-300)	0	Priority review vouchers have recently sold for \$125 million to \$350 million <sup>(5)</sup>

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

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

(3) 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

(4) 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 & Renshaw estimate peak 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-sustainable-profit>)

(5) 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-idUSKCN0QO1LQ20150819>). In Feb. 2017 Sarepta Therapeutics sold a priority review voucher to Gilead Sciences, Inc. for \$125 million (<http://fortune.com/2017/02/21/sarepta-gilead-review-voucher/>).

Table of Contents

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.

***Animal Health***

In the animal health space, we focus on developing and commercializing first-in-class gastrointestinal products for companion and production animals, foals, and high value horses.

Our pipeline currently includes prescription drug product candidates and non-prescription products targeting eight species. Neonorm Foal is an antidiarrheal product for newborn horses, which we launched in the United States in early 2016. Neonorm Calf is an antidiarrheal product for preweaned dairy calves, which we launched in the United States at the end of 2014. We are also developing a pipeline of prescription drug product candidates and non-prescription (non-drug) products to address unmet needs in animal health.

Neonorm is a standardized botanical extract derived from the *Croton lechleri* tree. The reception among users of Neonorm Calf and Neonorm Foal has been positive. In June 2017 we launched neonorm.com, a commercial website for both Neonorm products. As we announced on June 14, 2017, the Organic Materials Review Institute ("OMRI") has reviewed Neonorm Calf and determined that it is allowed for use in compliance with the U.S. Department of Agriculture National Organic Program. OMRI is an international nonprofit organization that determines which input products are allowed for use in organic production and processing.

Table of Contents

**Jaguar Animal Prescription Drug Product Candidates**

<b>Product Candidates</b>	<b>Species</b>	<b>Indication</b>	<b>Recent Developments</b>	<b>Anticipated Near-Term Milestones</b>
Canalevia	Dogs	Chemotherapy-induced diarrhea (CID)	Completed safety study with commercial formulation in June 2015	Commercial launch in 2019
			RXE and environmental impact technical sections accepted by CVM	
			Received MUMS designation	
	Dogs	Exercise-induced diarrhea (EID)	Completed safety study with commercial formulation in June 2015	Commercial launch in 2019
			FDA indicated that use of Canalevia for this indication qualifies as a "minor use"	

**Business Strategy**

Our goal is to become a leading human and animal pharmaceuticals 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 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, controls commercial rights for Mytesi for all indications, territories and patient populations globally. Mytesi is in development for multiple possible follow-on indications, including cancer therapy-related diarrhea; 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 as a second-generation anti-secretory agent for use in cholera patients.

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 Mytesi sales nationally. We also significantly expanded our internal national salesforce for Mytesi through the hire in key U.S. markets of ten sales representatives experienced in the sale of drugs to HIV physicians and gastroenterologists and a regional sales director. Our new sales representatives are





Table of Contents

based in and cover Miami/South Florida, Los Angeles/Palm Springs, New York, Houston, Chicago/St. Louis, Indianapolis, Kansas City, Alabama, Atlanta, San Francisco, DC, Pennsylvania, New Jersey, Delaware, Maryland, Mississippi and Louisiana. Seven of these sales representatives are former long-term employees of the HIV portfolio business of drugmaker Bristol-Myers Squibb, while the remainder of the team possess extensive experience in drug sales to both HIV healthcare providers and gastroenterologists.

With the goal of continuing to drive Mytesi sales and awareness nationwide, our plans for 2018 include plans to increase to a total of 20 sales representatives plus an additional regional sales manager, the initiation of new and extensive sales and marketing programs, advertising and promotional activities, direct-to-patient hub-service activities, the expected publication of supplemental data, and an increased focus on patient empowerment and educational programs for the important and neglected comorbidity of diarrhea in people living with HIV. Additionally, as stated above, we expect Napo's recently signed agreement with pharmacy services provider TPS to help streamline and expand nationwide patient access to Mytesi. The core benefits of the program, named Mytesi Direct , include streamlining prescription fulfillment for Mytesi in order to ensure that Mytesi users receive their prescription quickly, coordinating with other Napo programs such as the Mytesi Copay Savings Card and the NapoCares Patient Assistance Program to help ensure that patient out-of-pocket expenses for Mytesi are as low as possible, and improving Mytesi refill adherence through the transmission of renewal reminders to patients.

***Leverage our relationships with key opinion leaders regarding development of human and animal 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 KOL advisory program in some manner.

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

Although it is possible that we may enter into 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 commercial rights) in the field of gastrointestinal care and cancer in the long term.

***Strategically plan our portfolio in the animal health space***

Portfolio planning for the animal health space is of utmost importance to us, given the wide array of potential species-specific products and because we do not want animal-related research and development activities to divert significant financial resources while we are focusing on growing Mytesi sales and seeking to move our company towards profitability. Additional formulations and additional animal product expenditures will be considered from time to time as part of portfolio planning and prioritization in the context of the combined company. Canalevia is our lead veterinary prescription drug product candidate, intended for treatment of various forms of diarrhea in dogs. Our next expected veterinary product commercial launch will be for Equilevia, a personalized premium proprietary total gut health product for equine athletes, which will be non-prescription.

***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

Table of Contents

planned follow-on indications. Crofelemer manufacturing is being conducted at a new, multimillion-dollar commercial manufacturing facility that has been FDA-inspected and approved. 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 derisked the program as much as we believe we possibly can. We believe this approach will lead to better long-term outcomes for our products in development.

With the Merger effective, we believe that our newly combined company is poised to realize a number of synergistic, value adding benefits and an expanded pipeline of potential blockbuster human follow-on indications, a second-generation anti secretory agent, as well as a pipeline of important animal indications for crofelemer, upon which to build global partnerships.

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 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 for various gastrointestinal indications. SB-300 is a distinct and proprietary Jaguar pharmaceutical formulation of a standardized botanical extract, also sustainably derived from the *Croton lechleri* tree.

We believe SB-300, which has the same mechanism of action as crofelemer and is 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 SB-300 represents a long-term pipeline opportunity as a second-generation anti-secretory agent, on a global basis, for multiple gastro-intestinal 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.

Our human and animal 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 various forms of 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 supported by the merger.

Table of Contents

**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

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).

**Human Products in Development**

**Cancer Therapy-Related Diarrhea (CTD)**

**CTD is a common problem with a relevant mechanism for crofelemer**

**National Cancer Institute Criteria for Grading Severity of Diarrhea**

	<b>Grade 1</b>	<b>Grade 2</b>	<b>Grade 3</b>	<b>Grade 4</b>
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 enrolling patients in conjunction with Georgetown University. The primary objective of the

Table of Contents

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 enrolling patients 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 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 as 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. 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. 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 IBS-D as detailed below. We recognize that patients suffering from IBS-D or IBS-M may require a polypharmaceutical approach to their lifetime management of the disease, and are therefore working to develop a low risk study designed to optimize efforts to develop an approved formulation to address these unmet medical needs.

Table of Contents

**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  $\geq 4$  for  $< 25\%$  of days in a given week and  $\geq 30\%$  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 D-IBS 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

Table of Contents

dose-related differences in constipation. During the two-week treatment-free follow-up period symptoms approached baseline levels.

**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 d-IBS.

*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-point 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  $\geq 30\%$  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 exclusively 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.

**Orphan Drug: Short Bowel Syndrome (SBS)**

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

Table of Contents

Saudi Arabia, SBS occurs with much higher incidence. Napo recently visited with medical centers in this region.

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.

We have received orphan-drug status for Mytesi (crofelemer) for the SBS 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

***Completed Study Travelers' Diarrhea***

*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.

A total of 184 persons from the United States who acquired diarrhea in Jamaica or Mexico were enrolled in a double-blind, placebo-controlled study examining the effectiveness of three doses of crofelemer in reducing illness. Subjects were treated with 125 mg, 250 mg, or 500 mg crofelemer or a

Table of Contents

matching placebo four times a day for 2 days. Subjects kept daily diaries of symptoms and were seen each day for 3 days. Of the subjects, 169 (92%) were included in the efficacy analysis.

The most common etiological agent identified was enterotoxigenic *Escherichia coli*, found in 19% of subjects. The mean time interval from taking the first dose of medication until passage of the last unformed stool during 48-hour therapy (TLUS48) was 38.7 hours for the placebo group.

TLUS48 was shortened by crofelemer:  
30.6 h for the 125-mg dose group ( $p = 0.005$ );  
30.3 h for the 250-mg group; and  
32.6 h for the 500-mg group ( $p = 0.01$ ).

Treatment failures were seen in 29.3% in the placebo group compared with 7.3% ( $p = 0.01$ ), 4.3 ( $p = 0.002$ ), and 9.8 ( $p = 0.026$ ) in the three treatment groups. Crofelemer was well tolerated at all doses.

The study provided statistically significant results of crofelemer use for shortening the duration of travelers' diarrhea. This antisecretory approach works directly against the pathophysiology of travelers' diarrhea and is not likely to potentiate invasive forms of diarrhea or to produce posttreatment constipation.

**Cholera/General Watery Diarrhea**

According to the Centers for Disease Control and Prevention of the U.S. Department of Health & Human Services, Cholera is an acute, diarrheal illness caused by infection of the intestine with the bacterium *Vibrio cholerae*. An estimated 3-5 million cases and over 100,000 deaths occur each year around the world. The infection is often mild or without symptoms, but can sometimes be severe. Approximately one in 10 (5-10%) of infected persons will have severe disease characterized by profuse watery diarrhea, vomiting, and leg cramps. In these people, rapid loss of body fluids leads to dehydration and shock. Without treatment, death can occur within hours. At this time, for example, the largest cholera outbreak in recorded history is occurring in Yemen.

We are investigating SB-300 for the indication of cholera/general watery diarrhea. SB-300 is a distinct and proprietary Napo pharmaceutical formulation of a standardized botanical extract, also sustainably derived from the *Croton lechleri* tree. We believe SB-300 represents a long-term pipeline opportunity as a second-generation anti-secretory agent, on a global basis, for multiple gastro-intestinal diseases. Additionally, we believe SB-300, which has the same mechanism of action as crofelemer and is less costly to produce, may support efforts to receive a priority review voucher from the U.S. FDA for a cholera indication. Priority review vouchers are granted by the FDA to drug developers as an incentive to develop treatments for neglected diseases and rare pediatric diseases. If approved for this indication, SB-300 could serve as long-term pipeline anti-secretory agent for cholera/general watery diarrhea in geographies where cost of goods is a critical factor, for example, in resource-constrained regions and countries in which a requirement exists for drug prices to decrease annually.

**Clinical Study**

We have initiated CMC and have multiple animal and human studies in secretory diarrheas with SB-300. We have also completed a successful trial design for cholera with an anti-secretory mechanism of action, published studies with crofelemer in patients with cholera and other acute severe watery diarrhea disease.



Table of Contents

***Completed Studies Cholera and Severe Acute Dehydrating Watery Diarrhea***

*Phase 2 study of crofelemer in the treatment acute, severely dehydrating watery diarrhea with confirmed cholera with the use of an antibiotic (azithromycin) and oral rehydration therapy in 100 adult patients between 18 and 55 in Bangladesh.*

A total of 100 adult patients, from Bangladesh, between the ages of 18 and 55, with acute, severely dehydrating watery diarrhea with confirmed cholera were treated with crofelemer on a background of an antibiotic (azithromycin) and oral rehydration therapy. After a four-hour period of rapid rehydration therapy, patients were randomized 1:2:2 to placebo or 125 mg or 250 mg oral dose of crofelemer. Crofelemer or placebo doses were administered about one hour after the oral administration of azithromycin (1 gm dose). The primary objective was to evaluate the safety and effects of crofelemer on reducing the watery stool output normalized to body weight (mL/kg) in the first 24 hours on the background of azithromycin and rehydration therapy. Crofelemer was well tolerated and there were no drug related adverse events in this study. Both doses of crofelemer produced approximately 25-30% reduction in median watery stool volumes in the 0-6 and 0-12 hour period following initiation of therapy. Crofelemer showed a strong trend in the reduction of watery stool output in the 0-6 hour and 0-12 hour intervals ( $p=0.07$ ). Upon exclusion of three outlier patients, the crofelemer dose of 125 mg produced a statistically significant reduction in the normalized stool output ( $p=0.028$ ) and the dose of 250 mg crofelemer showed a strong trend for reduction of watery stool output ( $p=0.07$ ).

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

*Results:* 98 patients (51 crofelemer, 47 placebo) were enrolled in the study. 16 patients (4 in the crofelemer group and 12 in the placebo group) used antibiotics and were considered as treatment failures and were excluded from the "per protocol efficacy analysis". Groups were similar in age, weight, vital signs, stool frequency, consistency, dehydration and GI index.

The crofelemer group had improvement over baseline and compared to placebo at day 3. More specifically, crofelemer showed superior effects in reducing stool weight (61% vs 11%), stool frequency (65% vs 21%), reversion to soft stool (92% vs 49%) and improved the 7-item GI index (70% C vs 33% P), (all  $p<0.05$ ).

Crofelemer was well tolerated with no related serious adverse events or concerning changes in lab values. Progression to dehydration and report of fecal incontinence was more common in placebo group ( $p<0.05$ ).

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

Table of Contents

**Other Human Product Potential Future Indications**

**Institutional Diarrhea**

Patients in medical institutions such as hospitals often experience diarrhea following infection with *Clostridium difficile*, an anaerobic bacillus shed in feces. According to the Centers for Disease Control and Prevention of the U.S. Department of Health & Human Services, any surface, device, or material (e.g., commodes, bathing tubs, and electronic rectal thermometers) that becomes contaminated with feces may serve as a reservoir for the *C. difficile* spores, which are transferred to patients mainly via the hands of healthcare personnel who have touched a contaminated surface or item. We believe development of an approved formulation of crofelemer for use in *C. difficile* has the potential to help patients infected with *C. difficile* leave the hospital sooner, help keep patients infected with *C. difficile* out of the hospital, and aid in controlling *C. difficile* contagion in institutional settings, which would also represent a significant economic benefit.

**Animal Products in Development**

Since our July 2017 merger with Napo, as previously announced, Jaguar's human portfolio has been, and continues to be, our core focus. However, CID is an interesting model for human product performance and is being pursued as our first prescription indication for animal health under MUMS designation (we are also leveraging our MUMS regulatory package to include exercise induced diarrhea in dogs). We believe there is an important unmet medical need for the treatment of CID in dogs, and that Canalevia is an ideal treatment for this indication because of its demonstrated novel anti-secretory mechanism of action. We are also continuing initiatives related to Equilevia, our non-prescription, personalized, premium product for total gut health in equine athletes, and continuing fulfillment support for both Neonorm Foal and Neonorm Calf.

**Competition**

**Human Health**

There are several significantly larger pharmaceutical companies competing with us in the gastrointestinal segment. These companies include Valeant Pharmaceuticals International, Merck & Co., Inc., and Allergan plc as well as smaller pharmaceutical companies.

*Diarrhea in adult patients living with HIV/AIDS.* We are not aware of any other FDA-approved drugs for the symptomatic relief of diarrhea in HIV/AIDS patients. HIV/AIDS patients also use loperimide and over the counter anti-diarrheal remedies such as Mylanta or Kaopectate to treat their diarrhea, but these medicines affect motility and can result in rebound diarrhea.

*Diarrhea predominant irritable bowel syndrome.* Two drugs were approved in 2015 for the treatment of diarrhea predominant irritable bowel syndrome, Allergan plc's Virbezi and Xifaxan which is marketed by Valeant Pharmaceuticals International. Also, Lotronex was approved by the FDA in 2000 but was withdrawn from the market and later reintroduced in 2002 under a Risk Management Program. With the exception of Lotronex, the sponsors of Verbezi and Xifaxan employ extensive media and print promotion for the commercialization of these products. We are seeking a partner to further the clinical development and commercialization of crofelemer for d-IBS. There are currently numerous trials on going for d-IBS.

*Pediatric diarrhea.* Acute diarrhea in children is commonly treated by a change in diet, oral rehydration therapy and/or antibiotics, assuming the cause of the diarrhea is bacterial in nature. Children aged 12 and younger are advised not to use anti-motility drugs (loperamide for example) unless directed to do so by a physician. There are recent clinical trials for probiotics and zinc sulfate. Other recent anti-diarrheal studies in children include a safety and tolerability study of Fidaxomicin for *C difficile* associated diarrhea.

Table of Contents

*Chemotherapy induced diarrhea.* We are not aware of any FDA-approved drugs specifically indicated for chemotherapy induced diarrhea. A recent Phase IIb trial of elsiglutide for the treatment of chemotherapy induced diarrhea in colorectal cancer patients did not meet statistical significance. Opioids and over the counter drugs are commonly used to treat chemotherapy induced diarrhea, but these drugs affect motility. Certain tyrosine-kinase inhibitor chemotherapy agents have diarrhea as a significant side effect.

*Congenital Diarrheal Disorders and Short Bowel Syndrome.* We are not aware of any FDA-approved drugs specifically indicated for Congenital Diarrheal Disorders and Short Bowel Syndrome.

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

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

To our knowledge, there are currently no FDA-approved anti-secretory products, in particular which act locally in the gut with the chronic safety profile of crofelemer, in development or on the market. Crofelemer represents a new tool in gastro-intestinal disease management.

**Distribution and Marketing Agreements**

Napo has agreements in place with BexR, a distributor in Texas, and SmartPharma, a marketing and commercialization advisory firm, for the distribution, marketing and sale of Mytesi. The agreements compensate these parties with a percentage of net sales, as defined. Payments by Napo to BexR will be a specified percentage of net sales, ranging in the low double digits but in no instance exceeding 20% of net sales, depending on the period in which the sales occur and the amount of such sales. Payments by Napo to SmartPharma will be a specified percentage of net sales, ranging in the low double digits but in no instance exceeding 20% of net sales, depending on the amount of such sales. In addition, under certain circumstances, Napo will be required to pay SmartPharma a termination fee equal to a certain percentage of net sales generated within a specified period after the termination date.

**Manufacturing**

The plant material used to manufacture is crude plant latex ("CPL") extracted and purified from *Croton lechleri*, a widespread and naturally regenerating tree in the rainforest that is managed as part of sustainable harvesting programs. The tree is found in several South American countries and has been the focus of long-term sustainable harvesting research and development work. Napo's collaborating suppliers obtain CPL and arrange for the shipment of CPL to Napo's third-party contract manufacturer.

Napo's third-party contract manufacturer, India-based Glenmark Pharmaceuticals Ltd. (Glenmark), a research-driven, global, integrated pharmaceutical company, is Napo's primary manufacturer of crofelemer, the active pharmaceutical ingredient in Mytesi. Glenmark processes CPL into crofelemer utilizing a proprietary manufacturing process. The processing occurs at two FDA-approved Glenmark facilities. Additionally, Napo plans to establish a third processing site, which will be operated by Indena S.p.A., a Milan, Italy-based contract manufacturer dedicated to the identification, development and production of high-quality active principles derived from plants, for use in the pharmaceutical, health food and personal care industries. Indena has completed the required technology transfer and has equipment in place for pilot manufacturing.

Table of Contents

Canalevia will be manufactured by the same process used to manufacture the API that was used in the animal safety studies and the human studies in support of the approval of Mytesi. Napo has also licensed this intellectual property to third parties in connection with its licenses related to the development and commercialization of crofelemer for human use. While we believe these third parties have developed their own proprietary manufacturing specifications pursuant to their license agreements, such third-party intellectual property is unknown to us, and is not part of the intellectual property that we intend to use for the manufacture of API in its licensed field of use.

In May 2014 and June 2014, and as amended in February 2015, we entered into binding memorandums of understanding with Indena S.p.A. to negotiate a definitive commercial supply agreement for the manufacture of the API in Canalevia and the botanical extract in Neonorm. We have furnished equipment to Indena S.p.A. for use in a facility that will be dedicated to the manufacture of crofelemer and the botanical extract.

We have made all contractual payments to Indena as of March 31, 2016. In March 2015, Indena S.p.A. agreed to delay payment of the fees payable by the end of March 2015 until the earlier of April 30, 2015 or the completion of our initial public offering. In July 2015 and December 2015 Indena S.p.A. agreed to delay payment of certain fees payable until March 2016. In June 2014, as contemplated by the memorandums of understanding, we also issued Indena S.p.A. a warrant to acquire 16,666 shares our common stock at an exercise price per share equal to 90% of the initial public offering price, which expires in June 2019.

In September 2015 we entered a distribution agreement with Glenmark. With the execution of the agreement, we intend to use Glenmark as our primary manufacturer of crofelemer for animal health use. Our agreement with Glenmark supplements our previously announced manufacturing agreement with Indena S.p.A. for the standardized botanical extract in Neonorm Calf and Neonorm Foal. We intend to eventually use Indena as an alternative supplier for crofelemer.

In October 2015, we announced that we signed a crofelemer formulation development and manufacturing contract with Patheon Pharmaceuticals Inc. ("Patheon"), a leading global provider of drug development and delivery solutions to the global pharmaceutical and biopharma industries. Under the terms of the contract, Patheon will provide enteric-coated crofelemer tablets for us for use in animals. The tablets were used in our pivotal efficacy trial for Canalevia, which began in the fourth quarter of 2015.

Patheon is the manufacturer of Mytesi.

We also plan to enter agreements with third parties for the formulation of the API and botanical extracts into finished products to be used for planned studies and commercialization.

We plan to ensure that the facilities of our third-party contract manufacturers that will manufacture our API and botanical extract, as well as formulate our finished products, comply with cGMP and other relevant manufacturing requirements.

**Proprietary Library of Medicinal Plants**

We possess a proprietary library of more than 2,300 medicinal plants.

**Intellectual Property**

**Trademarks**

We plan to market all of our products under a trademark or trademarks we select and we will own all rights, title and interest, including all goodwill, associated with such trademarks. Mytesi is a registered trademark owned by Napo.

Table of Contents

**License Agreements**

***Termination, Asset Transfer and Transition Agreement***

On September 19, 2017 (the "Transfer Date"), Napo entered into the Termination, Asset Transfer and Transition Agreement (the "Glenmark Transition Agreement") with Glenmark. The Glenmark Transition Agreement supersedes the Glenmark Collaboration Agreement and returns to Napo certain rights which Napo licensed to Glenmark pursuant to the Glenmark Collaboration Agreement related to the development and commercialization of crofelemer for certain specified human indications in India and 140 other countries largely in developing regions (the "Transferred Assets").

As a result of the execution of the Glenmark Transition Agreement, we, through Napo, now control commercial rights for Mytesi for all indications, territories and patient populations globally, and also hold commercial rights to the existing regulatory approvals for crofelemer in Brazil, Ecuador, Zimbabwe and Botswana.

In consideration for Glenmark's assignment and transfer of the Transferred Assets to Napo, Napo agreed to pay Glenmark in cash, within 45 days after receipt by Napo, 25% of any payment that Napo receives from a third party to whom Napo grants a license or sublicense or with whom Napo partners in respect of, or sells or otherwise transfers any of the Transferred Assets, subject to certain limitations, until Glenmark has received a total of \$7 million. As additional consideration for the assignment and transfer of the Transferred Assets, Napo agreed (i) to enter into, within 90 days after the Transfer Date, a manufacturing and supply agreement with Glenmark for crofelemer, which will be manufactured at either or both of Glenmark's facilities in India and (ii) to transfer and assign to Glenmark all right, title and interest in and to certain required dedicated equipment used to manufacture crofelemer located at Glenmark's Ankleshwar facility, subject to certain limitations.

***License Agreement with Elanco US Inc.***

As we announced on January 31, 2017, we signed an agreement with Elanco US Inc. ("Elanco"), a subsidiary of Eli Lilly and Company, to license, develop, co-promote, and commercialize Canalevia, our drug product candidate under investigation for treatment of acute diarrhea and CID in dogs. The agreement granted Elanco exclusive global rights to Canalevia for use in companion animals. As we announced on November 1, 2017, we received notice from Elanco of its decision to terminate the License, Development Co-Promotion and Commercialization Agreement by giving Jaguar 90 days written notice. Pursuant to the terms of the agreement, termination of the agreement became effective January 30, 2018, 90 days after the date of the notice. On the effective date of termination of the agreement, all licenses granted to Elanco by Jaguar under the agreement were revoked and the rights granted thereunder reverted back to Jaguar.

**Patent Portfolio**

***Napo***

Napo owns a portfolio of patents and patent applications covering formulations of and methods of treatment with proanthocyanidin polymers isolated from *Croton spp* or *Calophyllum spp.*, including Mytesi (crofelemer). The patent family related to International Patent publication WO1998/16111 relates to enteric protected formulations of proanthocyanidin polymers isolated from *Croton spp* or *Calophyllum spp.*, including crofelemer, and methods of treating watery diarrhea using these enteric protected formulation. There are two U.S. patents in this family, including, US 7,323,195, which has a term until at least June 7, 2018, and US 7,341,744, which has a term until at least June 23, 2019. Napo has elected to extend the term of US 7,341,744 under 35 U.S.C. 156, and the United States Patent and Trademark Office has issued a Notice of Final Determination that the patent term extension for US 7,341,744 is 1075 days.

Table of Contents

Based upon the June 23, 2019 expiration date, the patent would be extended to June 2, 2022, to account for regulatory delay in obtaining human marketing approval for crofelemer.

Napo additionally owns a family of patents arising from International Patent Application Publication WO2012058664 that cover methods of treating HIV associated diarrhea and HAART associated diarrhea with proanthocyanidin polymers isolated from *Croton spp* or *Calophyllum spp.*, including crofelemer. In the U.S., there are two issued patents, US 8,962,680 and US 9,585,868, both of which expire October 31, 2031. Outside the U.S., patent protection for methods of treating HIV associated diarrhea has been obtained in Australia, Europe, Hong Kong, Japan, Kenya, Mexico, Russia, Ukraine, South Africa and Zimbabwe, with expiration dates of October 31, 2031, and Napo has pending applications in Brazil, Canada, China, India, Japan, Mexico, and Malaysia. Napo also has patent families related to methods of treating diarrhea predominant irritable bowel syndrome, constipation predominant irritable bowel syndrome, and inflammatory bowel disease, familial adenomatous polyposis and colon cancer, with proanthocyanidin polymers isolated from *Croton spp* or *Calophyllum spp.*, including crofelemer. In particular, for diarrhea predominant irritable bowel syndrome, Napo has 1 issued US patent, which expires February 9, 2027, and 1 pending application, issued patents in Australia, Europe, Japan, South Korea, Mexico, New Zealand, Singapore, and Taiwan and pending applications in Bangladesh, Bolivia, Canada, Chile, Gulf States, Mexico, Panama, Peru, Paraguay, Thailand, and Venezuela, all of which are estimated to expire April 30, 2027; for constipation predominant irritable bowel syndrome, Napo has 3 issued US patents, with terms of at least April 30, 2027, patents in Australia, Canada, Europe, Mexico, New Zealand, Singapore and a pending application in India, all of which are estimated to expire April 30, 2027; and for inflammatory bowel disease, familial adenomatous polyposis and/or colon cancer, Napo has 1 issued US patent, which has an expiration date of October 9, 2029 and 1 pending application, issued patents in Australia, Europe and a pending application in Canada, which have estimated expiration dates of April 30, 2027.

Napo also co-owns with Glenmark, issued patents in India, South Africa and Eurasia patents that expire August 24, 2030, and cover a method of manufacturing with proanthocyanidin polymers isolated from *Croton spp* or *Calophyllum spp.*, including crofelemer). Napo holds two US patents covering a formulation of NP 500 (nordihydroguaiaretic acid (NDGA)) and its use in treating a metabolic disorder that have terms until April 23, 2031 Napo has filed a US non-provisional application for the treatment of chemotherapy-induced diarrhea (CID) with crofelemer and two US provisional applications on other human indications.

**Jaguar**

We have exclusive rights in the veterinary field to an international patent family related to International Patent Application WO1998/16111 as set forth above in the disclosure of the Napo patent portfolio. The patents in this family are directed to enteric protected formulations of proanthocyanidin polymers isolated from *Croton spp* or *Calophyllum spp.* (such as crofelemer and Neonorm), and methods of treating watery diarrhea using the enteric protected formulations for both human and veterinary uses. As such, the patents of this family cover certain formulations of crofelemer, including Canalevia, as well as the standardized botanical extract in Neonorm, and methods of treating diarrhea using these formulations.

Certain Napo patents and patent applications, which cover both human and veterinary uses, were previously licensed by Napo to Salix for certain fields of human use. On March 4, 2016, Napo and Salix settled litigation and all rights to crofelemer and Mytesi (formerly known as Fulyzaq) were returned to Napo and the collaboration agreement between Salix and Napo (the "Salix Collaboration Agreement"), was terminated. Napo has the responsibility to file, prosecute and maintain the Napo Patents. There are two issued Napo Patents in the United States that cover, collectively, enteric protected formulations of proanthocyanidin polymers isolated from *Croton spp.* and methods of treating watery diarrhea using the enteric protected formulations for both human and veterinary uses.

Table of Contents

We have filed and have currently three applications pending under the PCT, and seven U.S. non provisional patent applications relating to veterinary uses of *Croton* proanthocyanidin polymer compositions, including crofelemer, Neonorm and Canalevia, and product combinations under development. These applications are directed to treatment of watery diarrhea in newborn and young animals, including methods of improving mortality and weight gain in newborn animals, treatment of stress induced diarrhea in animals, and treatment of watery diarrhea caused by salmonella in animals. These applications also focus on the treatment of diarrhea in companion animals such as dogs and cats. In addition, an application has been submitted for the treatment of ulcers and related symptoms in animals with an emphasis on ulcers in horses. An application has also been filed on a prebiotic effect of crofelemer in bovine and other animal species based on research findings that indicate a prebiotic enhancement of the gut bacteria in animals. One other patent application has been filed combining crofelemer with rifaximin, a non absorbed antibiotic for the treatment of bacteria induced diarrhea in multiple animal species. Applications have been filed relating to treatment of porcine epidemic virus in piglets and treatment of diarrhea in livestock with a formulation that is not enteric protected. Patents that may issue based upon these applications should have terms that extend until at least May 2035.

**Government Regulation**

***Human Health Business***

The FDA and comparable regulatory authorities in state and local jurisdictions and in other countries impose substantial and burdensome requirements upon companies involved in the clinical development, manufacture, marketing and distribution of prescription drugs such as those Napo is developing. These agencies and other federal, state and local entities regulate, among other things, the research and development, testing, manufacture, quality control, safety, effectiveness, labeling, storage, record keeping, approval, advertising and promotion, distribution, post-approval monitoring and reporting, sampling and export and import of Napo's drug product candidates. To comply with the regulatory requirements in each of the jurisdictions in which Napo is seeking to market and subsequently sell its prescription products, Napo is establishing processes and resources to provide oversight of the development, approval processes and launch of its products and to position those products in order to gain market share.

***U.S. Government Regulation***

In the United States, the FDA approves and regulates drugs under the Federal Food, Drug, and Cosmetic Act ("FDCA"), and its implementing regulations.

The process of obtaining regulatory approvals and the subsequent compliance with applicable federal, state, local and foreign statutes and regulations requires the expenditure of substantial time and financial resources. Failure to comply with the applicable U.S. requirements at any time during the product development process, approval process or after approval, may subject an applicant to a variety of administrative or judicial sanctions, such as the FDA's refusal to approve pending NDAs, withdrawal of an approval, imposition of a clinical hold, issuance of warning letters, product recalls, product seizures, total or partial suspension of production or distribution, injunctions, fines, refusals of government contracts, restitution, disgorgement or civil or criminal penalties.

The process required by the FDA before a drug may be marketed in the United States generally involves the following:

completion of pre-clinical laboratory tests, animal studies and formulation studies in compliance with the FDA's good laboratory practice, or GLP, regulations;

submission to the FDA of an investigational new drug application, or IND, which must become approved before human clinical trials may begin;

Table of Contents

approval by an institutional review board, or IRB, of the study protocol and informed consent forms for the clinical site before each trial may be initiated. Multiple sites may necessitate the involvement of multiple IRBs and submissions;

performance of adequate and well-controlled human clinical trials in accordance with good clinical practice, or GCP, requirements to establish the safety and efficacy of the proposed drug product for each indication;

submission to the FDA of an NDA which would include the study reports of the clinical trials, chemistry and manufacturing of the active pharmaceutical ingredient and the final dosage form as well as other required sections to be included in the NDA;

satisfactory completion of an FDA advisory committee review, if applicable;

satisfactory completion of an FDA inspection of the manufacturing facility or facilities at which the product is produced to assess compliance with current good manufacturing practice, or cGMP, requirements and to assure that the facilities, methods and controls are adequate to preserve the drug's identity, strength, quality and purity; and

FDA review and approval of the NDA.

*Pre-clinical Studies*

Pre-clinical studies include laboratory evaluation of the drug product's chemistry, toxicity and formulation, as well as animal studies to assess potential safety and efficacy. An IND sponsor must submit the results of the pre-clinical tests, together with manufacturing information, analytical data and any available clinical data or literature, among other things, to the FDA as part of an IND. Some pre-clinical testing may continue even after the IND is submitted. An IND automatically becomes effective 30 days after receipt by the FDA, unless before that time the FDA raises concerns or questions related to one or more proposed clinical trials and places the clinical trial on a clinical hold. In such a case, the IND sponsor and the FDA must resolve any outstanding concerns before the clinical trial can begin. As a result, submission of an IND may not result in the FDA allowing clinical trials to commence.

*Clinical Trials*

Clinical trials involve the administration of the investigational new drug to human subjects pursuant to a clinical protocol, under the supervision of qualified investigators in accordance with GCP requirements, which include the requirement that all research subjects provide their informed consent in writing for their participation in any clinical trial. Clinical trials are conducted under protocols detailing, among other things, the objectives or endpoints of the trial, the parameters to be used in monitoring safety, and the effectiveness criteria to be evaluated. A protocol for each clinical trial and any subsequent protocol amendments must be submitted to the FDA under the IND. In addition, an IRB at each institution participating in the clinical trial must review and approve the plan for any clinical trial before it commences at that institution. Information about certain clinical trials must be submitted within specific timeframes to the National Institutes of Health, or NIH, for public dissemination on their [www.clinicaltrials.gov](http://www.clinicaltrials.gov) website.

Human clinical trials are typically conducted in three sequential phases, which may overlap or be combined:

Phase 1: The drug is initially introduced into healthy human subjects or patients with the target disease or condition and tested for safety, dosage tolerance, absorption, metabolism, distribution, excretion and, if possible, to gain an early indication of its effectiveness depending on the endpoints set forth in the protocol.



Table of Contents

Phase 2: The drug is administered to a limited patient population to identify possible adverse effects and safety risks, to preliminarily evaluate the efficacy of the product for specific targeted diseases and to determine dosage tolerance and optimal dosage.

Phase 3: The drug is administered to an expanded patient population, generally at geographically dispersed clinical trial sites, in well-controlled clinical trials to generate enough data to statistically evaluate the efficacy and safety of the product for approval, to establish the overall risk-benefit profile of the product, and to provide adequate information for the labeling of the product.

Progress reports detailing the results of the clinical trials must be submitted at least annually to the FDA and more frequently if serious adverse events occur. Phase 1, Phase 2 and Phase 3 clinical trials may not be completed successfully within any specified period, or at all. Furthermore, the FDA or the sponsor may suspend or terminate a clinical trial at any time on various grounds, including a finding that the research subjects are being exposed to an unacceptable health risk. Similarly, an IRB can suspend or terminate approval of a clinical trial at its institution if the clinical trial is not being conducted in accordance with the IRB's requirements or if the drug has been associated with unexpected serious harm to patients.

*Special Protocol Assessment*

The special protocol assessment, or SPA, process is designed to facilitate the FDA's review and approval of drugs by allowing the FDA to evaluate issues related to the adequacy of certain clinical trials, including Phase 3 clinical trials that can form the primary basis for a drug product's efficacy claim in an NDA. Upon specific request by a clinical trial sponsor, the FDA will evaluate the protocol and respond to a sponsor's questions regarding, among other things, primary efficacy endpoints, trial conduct and data analysis, within 45 days of receipt of the request.

The FDA ultimately assesses whether the protocol design and planned analysis of the trial are acceptable to support regulatory approval of the product candidate with respect to effectiveness of the indication studied. All agreements and disagreements between the FDA and the sponsor regarding an SPA must be clearly documented in an SPA letter or the minutes of a meeting between the sponsor and the FDA.

Even if the FDA agrees to the design, execution and analyses proposed in protocols reviewed under the SPA process, the FDA may revoke or alter its agreement under the following circumstances:

public health concerns emerge that were unrecognized at the time of the protocol assessment;

the director of the review division determines that a substantial scientific issue essential to determining safety or efficacy has been identified after testing has begun;

a sponsor fails to follow a protocol that was agreed upon with the FDA; or

the relevant data, assumptions, or information provided by the sponsor in a request for SPA change, are found to be false statements or misstatements, or are found to omit relevant facts.

A documented SPA may be modified, and such modification will be deemed binding on the FDA review division, except under the circumstances described above, if FDA and the sponsor agree in writing to modify the protocol and such modification is intended to improve the study.

*Marketing Approval*

Assuming successful completion of the required clinical testing, the results of the pre-clinical studies and clinical trials, together with detailed information relating to the product's chemistry, manufacture, controls and proposed labeling, among other things, are submitted to the FDA as part of a NDA requesting approval to market the product for one or more indications. In most cases, the submission of a NDA is subject to a substantial application user fee. Under the Prescription Drug User Fee Act



Table of Contents

("PDUFA"), guidelines that are currently in effect, the FDA has a goal of ten months from the date of "filing" of a standard NDA for a new molecular entity to review and act on the submission. This review typically takes twelve months from the date the NDA is submitted to FDA because the FDA has approximately two months to make a "filing" decision.

In addition, under the Pediatric Research Equity Act of 2003 ("PREA"), as amended and reauthorized, certain NDAs or supplements to an NDA must contain data that are adequate to assess the safety and effectiveness of the drug for the claimed indications in all relevant pediatric subpopulations; this would include information which supports dosing and administration for each pediatric subpopulation for which the product is safe and effective. The FDA may, on its own initiative or at the request of the applicant, grant deferrals for submission of some or all pediatric data until after approval of the product for use in adults or full or partial waivers from the pediatric data requirements.

The FDA may also require submission of a risk evaluation and mitigation strategy, or REMS, plan to ensure that the benefits of the drug outweigh its risks. The REMS plan could include medication guides, physician communication plans, assessment plans, and/or elements to assure safe use, such as restricted distribution methods, patient registries, or other risk minimization tools.

The FDA may also require other information as part of the NDA filing such as an environmental impact statement. The FDA can waive some or delay compliance with some of these requirements.

The FDA conducts a preliminary review of all NDAs within the first 60 days after submission, before accepting them for filing, to determine whether they are sufficiently complete to permit substantive review. The FDA may request additional information rather than accept a NDA for filing. In this event, the application must be resubmitted with the additional information. The resubmitted application is also subject to review before the FDA accepts it for filing. Once the submission is accepted for filing, the FDA begins an in-depth substantive review. The FDA reviews a NDA to determine, among other things, whether the drug is safe and effective and whether the facility in which it is manufactured, processed, packaged or held meets standards designed to assure the product's continued safety, quality and purity.

The FDA may refer an application for a novel drug to an advisory committee. An advisory committee is a panel of independent experts, including clinicians and other scientific experts, that reviews, evaluates and provides a recommendation as to whether the application should be approved and under what conditions. The FDA is not bound by the recommendations of an advisory committee, but it considers such recommendations carefully when making decisions.

Before approving an NDA, the FDA typically will inspect the facility or facilities where the product is manufactured. The FDA will not approve an application unless it determines that the manufacturing processes and facilities are in compliance with cGMP requirements and adequate to assure consistent production of the product within required specifications. Additionally, before approving a NDA, the FDA may inspect one or more clinical trial sites to assure compliance with GCP requirements.

After evaluating the NDA and all related information, including the advisory committee recommendation, if any, and inspection reports regarding the manufacturing facilities and clinical trial sites, the FDA may issue an approval letter, or, in some cases, a complete response letter. A complete response letter must contain a statement of specific items that prevent the FDA from approving the application and will also contain conditions that must be met in order to secure final approval of the NDA and may require additional clinical or pre-clinical testing in order for FDA to reconsider the application. Even with submission of this additional information, the FDA ultimately may decide that the application does not satisfy the regulatory criteria for approval. If and when those conditions have been met to the FDA's satisfaction, the FDA will typically issue an approval letter. An approval letter authorizes commercial marketing of the drug with specific prescribing information for specific indications.

Even if the FDA approves a product, it may limit the approved indications for use of the product, require that contraindications, warnings or precautions be included in the product labeling, require that

Table of Contents

post-approval studies, Phase 4 clinical trials, be conducted to further assess a drug's safety after approval, require testing and surveillance programs to monitor the product after commercialization, or impose other conditions, including distribution and use restrictions or other risk management mechanisms under a REMS, which can materially affect the potential market and profitability of the product. The FDA may prevent or limit further marketing of a product based on the results of post-marketing studies or surveillance programs. After approval, some types of changes to the approved product, such as adding new indications, manufacturing changes, and additional labeling claims, are subject to further testing requirements and FDA review and approval.

*Post-Approval Requirements*

Drugs manufactured or distributed pursuant to FDA approvals are subject to pervasive and continuing regulation by the FDA, including, among other things, requirements relating to recordkeeping, periodic reporting, product sampling and distribution, advertising and promotion and reporting of adverse experiences with the product. After approval, most changes to the approved product, such as adding new indications or other labeling claims are subject to prior FDA review and approval. New secondary indications must be supported by clinical trials or data. There also are continuing, annual user fee requirements for any marketed products and the establishments at which such products are manufactured, as well as new application fees for supplemental applications with clinical data.

The FDA may impose a number of post-approval requirements as a condition of approval of an NDA. For example, the FDA may require post-marketing testing, including Phase 4 clinical trials, and surveillance to further assess and monitor the product's safety and effectiveness after commercialization.

In addition, drug manufacturers and other entities involved in the manufacture and distribution of approved drugs are required to register their establishments with the FDA and state agencies, and are subject to periodic unannounced inspections by the FDA and these state agencies for compliance with cGMP requirements. Changes to the manufacturing process are strictly regulated and often require prior FDA approval before being implemented. FDA regulations also require investigation and correction of any deviations from cGMP requirements and impose reporting and documentation requirements upon the sponsor and any third-party manufacturers that the sponsor may decide to use. Accordingly, manufacturers must continue to expend time, money and effort in the area of production and quality control to maintain cGMP compliance.

Once an approval is granted, the FDA may withdraw the approval if compliance with regulatory requirements and standards is not maintained or if problems occur after the product reaches the market. Later discovery of previously unknown problems with a product, including adverse events of unanticipated severity or frequency, or with manufacturing processes, or failure to comply with regulatory requirements, may result in mandatory revisions to the approved labeling to add new safety information; imposition of post-market studies or clinical trials to assess new safety risks; or imposition of distribution or other restrictions under a REMS program. Other potential consequences include, include, but are not limited to:

restrictions on the marketing or manufacturing of the product, complete withdrawal of the product from the market or product recalls;

fines, warning letters or holds on post-approval clinical trials;

refusal of the FDA to approve pending NDAs or supplements to approved NDAs, or suspension or revocation of product approvals;

product seizure or detention, or refusal to permit the import or export of products; or

injunctions or the imposition of civil or criminal penalties.

The FDA strictly regulates marketing, labeling, advertising and promotion of products that are placed on the market. Drugs may be promoted only for the approved indications and in accordance with the provisions of the approved label. The FDA and other agencies actively enforce the laws and regulations

Table of Contents

prohibiting the promotion of off-label uses, and a company that is found to have improperly promoted off-label uses may be subject to significant liability. In addition, the FDA regulates the purity and or consistency of the approved product. Products, if deemed adulterated can lead to serious consequences as set forth above as well as civil and criminal penalties.

***Foreign Government Regulation***

To the extent that any of Napo's product candidates, once approved, are sold in a foreign country, Napo may be subject to similar foreign laws and regulations, which may include, for instance, applicable post-marketing requirements, including safety surveillance, anti-fraud and abuse laws and implementation of corporate compliance programs and reporting of payments or other transfers of value to healthcare professionals.

In order to market Napo's future products in the EEA (which is comprised of the 28 Member States of the EU plus Norway, Iceland and Liechtenstein) and many other foreign jurisdictions, a sponsor must obtain separate regulatory approvals. More concretely, in the EEA, medicinal products can only be commercialized after obtaining a Marketing Authorization, or MA. There are two types of marketing authorizations:

the Community MA, which is issued by the European Commission through the Centralized Procedure, based on the opinion of the Committee for Medicinal Products for Human Use of the European Medicines Agency, or EMA, and which is valid throughout the entire territory of the EEA. The Centralized Procedure is mandatory for certain types of products, such as biotechnology medicinal products, orphan medicinal products and medicinal products indicated for the treatment of AIDS, cancer, neurodegenerative disorders, diabetes, auto-immune and viral diseases. The Centralized Procedure is optional for products containing a new active substance not yet authorized in the EEA, or for products that constitute a significant therapeutic, scientific or technical innovation or which are in the interest of public health in the EU; and

National MAs, which are issued by the competent authorities of the Member States of the EEA and only cover their respective territory, are available for products not falling within the mandatory scope of the Centralized Procedure. Where a product has already been authorized for marketing in a Member State of the EEA, this National MA can be recognized in another Member State through the Mutual Recognition Procedure. If the product has not received a National MA in any Member State at the time of application, it can be approved simultaneously in various Member States through the Decentralized Procedure.

Under the above described procedures, before granting the MA, the EMA or the competent authorities of the Member States of the EEA make an assessment of the risk-benefit balance of the product on the basis of scientific criteria concerning its quality, safety and efficacy.

In the EEA, new products authorized for marketing, or reference products, qualify for eight years of data exclusivity and an additional two years of market exclusivity upon marketing authorization. The data exclusivity period prevents generic or biosimilar applicants from relying on the pre-clinical and clinical trial data contained in the dossier of the reference product when applying for a generic or biosimilar marketing authorization in the EU during a period of eight years from the date on which the reference product was first authorized in the EU. The market exclusivity period prevents a successful generic or biosimilar applicant from commercializing its product in the EU until 10 years have elapsed from the initial authorization of the reference product in the EU. The 10-year market exclusivity period can be extended to a maximum of eleven years if, during the first eight years of those 10 years, the marketing authorization holder obtains an authorization for one or more new therapeutic indications which, during the scientific evaluation prior to their authorization, are held to bring a significant clinical benefit in comparison with existing therapies.

Table of Contents

In the EEA, marketing authorization applications for new medicinal products not authorized have to include the results of studies conducted in the pediatric population, in compliance with a pediatric investigation plan, or PIP, agreed with the EMA's Pediatric Committee ("PDCO"). The PIP sets out the timing and measures proposed to generate data to support a pediatric indication of the drug for which marketing authorization is being sought. The PDCO can grant a deferral of the obligation to implement some or all of the measures of the PIP until there are sufficient data to demonstrate the efficacy and safety of the product in adults. Further, the obligation to provide pediatric clinical trial data can be waived by the PDCO when these data is not needed or appropriate because the product is likely to be ineffective or unsafe in children, the disease or condition for which the product is intended occurs only in adult populations, or when the product does not represent a significant therapeutic benefit over existing treatments for pediatric patients. Once the marketing authorization is obtained in all Member States of the EU and study results are included in the product information, even when negative, the product is eligible for six months' supplementary protection certificate extension. For orphan-designated medicinal products, the 10-year period of market exclusivity is extended to 12 years.

***Other U.S. Healthcare Laws***

In addition to FDA restrictions on marketing of pharmaceutical and biological products, other U.S. federal and state healthcare regulatory laws restrict business practices in the pharmaceutical industry, which include, but are not limited to, state and federal anti-kickback, false claims, data privacy and security and physician payment and drug pricing transparency laws.

The U.S. federal Anti-Kickback Statute prohibits, among other things, any person or entity from knowingly and willfully offering, paying, soliciting, receiving or providing any remuneration, directly or indirectly, overtly or covertly, to induce or in return for purchasing, leasing, ordering, or arranging for or recommending the purchase, lease, or order of any good, facility, item or service reimbursable, in whole or in part, under Medicare, Medicaid or other federal healthcare programs. The term "remuneration" has been broadly interpreted to include anything of value. The Anti-Kickback Statute has been interpreted to apply to arrangements between pharmaceutical manufacturers on the one hand and prescribers, purchasers, formulary managers and beneficiaries on the other. Although there are a number of statutory exceptions and regulatory safe harbors protecting some common activities from prosecution, the exceptions and safe harbors are drawn narrowly. Practices that involve remuneration that may be alleged to be intended to induce prescribing, purchases, or recommendations may be subject to scrutiny if they do not meet the requirements of a statutory or regulatory exception or safe harbor. Failure to meet all of the requirements of a particular applicable statutory exception or regulatory safe harbor does not make the conduct per se illegal under the U.S. federal Anti-Kickback Statute. Instead, the legality of the arrangement will be evaluated on a case-by-case basis based on a cumulative review of all its facts and circumstances. Several courts have interpreted the statute's intent requirement to mean that if any one purpose of an arrangement involving remuneration is to induce referrals of federal healthcare covered business, the statute has been violated.

Additionally, the intent standard under the U.S. federal Anti-Kickback Statute was amended by the Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act of 2010, or collectively, the ACA, to a stricter standard such that a person or entity does not need to have actual knowledge of the statute or specific intent to violate it in order to have committed a violation. In addition, the ACA codified case law that a claim including items or services resulting from a violation of the U.S. federal Anti-Kickback Statute constitutes a false or fraudulent claim for purposes of the federal civil False Claims Act. The majority of states also have anti-kickback laws, which establish similar prohibitions and in some cases may apply to items or services reimbursed by any third-party payor, including commercial insurers.

The federal false claims and civil monetary penalties laws, including the civil False Claims Act, prohibit any person or entity from, among other things, knowingly presenting, or causing to be presented, a

Table of Contents

false, fictitious or fraudulent claim for payment to, or approval by, the federal government, knowingly making, using, or causing to be made or used a false record or statement material to a false or fraudulent claim to the federal government, or from knowingly making a false statement to avoid, decrease or conceal an obligation to pay money to the U.S. federal government. A claim includes "any request or demand" for money or property presented to the U.S. government. Actions under the civil False Claims Act may be brought by the Attorney General or as a qui tam action by a private individual in the name of the government. Violations of the civil False Claims Act can result in very significant monetary penalties and treble damages. Several pharmaceutical and other healthcare companies have been prosecuted under these laws for, among other things, allegedly providing free product to customers with the expectation that the customers would bill federal programs for the product. Other companies have been prosecuted for causing false claims to be submitted because of the companies' marketing of products for unapproved, or off-label, uses. In addition, the civil monetary penalties statute imposes penalties against any person who is determined to have presented or caused to be presented a claim to a federal health program that the person knows or should know is for an item or service that was not provided as claimed or is false or fraudulent. Many states also have similar fraud and abuse statutes or regulations that apply to items and services reimbursed under Medicaid and other state programs, or, in several states, apply regardless of the payor.

Violations of fraud and abuse laws, including federal and state anti-kickback and false claims laws, may be punishable by criminal and civil sanctions, including fines and civil monetary penalties, the possibility of exclusion from federal healthcare programs (including Medicare and Medicaid), disgorgement and corporate integrity agreements, which impose, among other things, rigorous operational and monitoring requirements on companies. Similar sanctions and penalties, as well as imprisonment, also can be imposed upon executive officers and employees of such companies. Given the significant size of actual and potential settlements, it is expected that the government authorities will continue to devote substantial resources to investigating healthcare providers' and manufacturers' compliance with applicable fraud and abuse laws.

The federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, created additional federal criminal statutes that prohibit, among other actions, knowingly and willfully executing, or attempting to execute, a scheme to defraud any healthcare benefit program, including private third-party payors, knowingly and willfully embezzling or stealing from a healthcare benefit program, willfully obstructing a criminal investigation of a healthcare offense and knowingly and willfully falsifying, concealing or covering up a material fact or making any materially false, fictitious or fraudulent statement in connection with the delivery of or payment for healthcare benefits, items or services. Similar to the U.S. federal Anti-Kickback Statute, the ACA broadened the reach of certain criminal healthcare fraud statutes created under HIPAA by amending the intent requirement such that a person or entity does not need to have actual knowledge of the statute or specific intent to violate it in order to have committed a violation.

In addition, there has been a recent trend of increased federal and state regulation of payments made to physicians and certain other healthcare providers. The ACA imposed, among other things, new annual reporting requirements through the Physician Payments Sunshine Act for covered manufacturers for certain payments and "transfers of value" provided to physicians and teaching hospitals, as well as ownership and investment interests held by physicians and their immediate family members. Failure to submit timely, accurately and completely the required information for all payments, transfers of value and ownership or investment interests may result in civil monetary penalties of up to an aggregate of \$150,000 per year and up to an aggregate of \$1 million per year for "knowing failures." Covered manufacturers must submit reports by the 90th day of each subsequent calendar year. In addition, certain states require implementation of compliance programs and compliance with the pharmaceutical industry's voluntary compliance guidelines and the relevant compliance guidance promulgated by the federal government, impose restrictions on marketing practices and/or tracking and reporting of gifts, compensation and other remuneration or items of value provided to physicians and other healthcare professionals and entities.

Table of Contents

Napo may also be subject to data privacy and security regulation by both the federal government and the states in which Napo conducts its business. HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act, or HITECH, and their respective implementing regulations, including the Final HIPAA Omnibus Rule published on January 25, 2013, impose specified requirements relating to the privacy, security and transmission of individually identifiable health information held by covered entities and their business associates. Among other things, HITECH made HIPAA's security standards directly applicable to "business associates," defined as independent contractors or agents of covered entities that create, receive, maintain or transmit protected health information in connection with providing a service for or on behalf of a covered entity. HITECH also increased the civil and criminal penalties that may be imposed against covered entities, business associates and possibly other persons, and gave state attorneys general new authority to file civil actions for damages or injunctions in federal courts to enforce the federal HIPAA laws and seek attorney's fees and costs associated with pursuing federal civil actions. In addition, state laws govern the privacy and security of health information in certain circumstances, many of which differ from each other in significant ways and may not have the same requirements, thus complicating compliance efforts.

***Coverage and Reimbursement***

Significant uncertainty exists as to the coverage and reimbursement status of any pharmaceutical products for which Napo obtains regulatory approval. In the United States and markets in other countries, patients who are prescribed treatments for their conditions and providers performing the prescribed services generally rely on third-party payors to reimburse all or part of the associated healthcare costs. Patients are unlikely to use Napo's products unless coverage is provided and reimbursement is adequate to cover a significant portion of the cost of Napo's products. Sales of any products for which Napo receives regulatory approval for commercial sale will therefore depend, in part, on the availability of coverage and adequate reimbursement from third-party payors. Third-party payors include government authorities, managed care plans, private health insurers and other organizations. In the United States, the process for determining whether a third-party payor will provide coverage for a pharmaceutical or biological product typically is separate from the process for setting the price of such product or for establishing the reimbursement rate that the payor will pay for the product once coverage is approved. Third-party payors may limit coverage to specific products on an approved list, also known as a formulary, which might not include all of the FDA-approved products for a particular indication. A decision by a third-party payor not to cover Napo's product candidates could reduce physician utilization of Napo's products once approved and have a material adverse effect on Napo's sales, results of operations and financial condition. Moreover, a third-party payor's decision to provide coverage for a pharmaceutical or biological product does not imply that an adequate reimbursement rate will be approved. Adequate third-party reimbursement may not be available to enable Napo to maintain price levels sufficient to realize an appropriate return on Napo's investment in product development. Additionally, coverage and reimbursement for products can differ significantly from payor to payor. One third-party payor's decision to cover a particular medical product or service does not ensure that other payors will also provide coverage for the medical product or service, or will provide coverage at an adequate reimbursement rate. As a result, the coverage determination process will require Napo to provide scientific and clinical support for the use of Napo's products to each payor separately and will be a time-consuming process.

In the EEA, governments influence the price of products through their pricing and reimbursement rules and control of national health care systems that fund a large part of the cost of those products to consumers. Some jurisdictions operate positive and negative list systems under which products may only be marketed once a reimbursement price has been agreed to by the government. To obtain reimbursement or pricing approval, some of these countries may require the completion of clinical trials that compare the cost effectiveness of a particular product candidate to currently available therapies. Other member states allow companies to fix their own prices for medicines, but monitor and control company profits. The downward pressure on health care costs in general, particularly prescription products, has become very



Table of Contents

intense. As a result, increasingly high barriers are being erected to the entry of new products. In addition, in some countries, cross border imports from low-priced markets exert a commercial pressure on pricing within a country.

The containment of healthcare costs has become a priority of federal, state and foreign governments, and the prices of pharmaceutical or biological products have been a focus in this effort. Third-party payors are increasingly challenging the prices charged for medical products and services, examining the medical necessity and reviewing the cost-effectiveness of pharmaceutical or biological products, medical devices and medical services, in addition to questioning safety and efficacy. If these third-party payors do not consider Napo's products to be cost-effective compared to other available therapies, they may not cover Napo's products after FDA approval or, if they do, the level of payment may not be sufficient to allow Napo to sell its products at a profit.

***Healthcare Reform***

A primary trend in the U.S. healthcare industry and elsewhere is cost containment. Government authorities and other third-party payors have attempted to control costs by limiting coverage and the amount of reimbursement for particular medical products. For example, in March 2010, the ACA was enacted, which, among other things, increased the minimum Medicaid rebates owed by most manufacturers under the Medicaid Drug Rebate Program; introduced a new methodology by which rebates owed by manufacturers under the Medicaid Drug Rebate Program are calculated for drugs that are inhaled, infused, instilled, implanted or injected; extended the Medicaid Drug Rebate Program to utilization of prescriptions of individuals enrolled in Medicaid managed care plans; imposed mandatory discounts for certain Medicare Part D beneficiaries as a condition for manufacturers' outpatient drugs coverage under Medicare Part D; subjected drug manufacturers to new annual fees based on pharmaceutical companies' share of sales to federal healthcare programs; created a new Patient Centered Outcomes Research Institute to oversee, identify priorities in, and conduct comparative clinical effectiveness research, along with funding for such research; creation of the Independent Payment Advisory Board, once empaneled, will have authority to recommend certain changes to the Medicare program that could result in reduced payments for prescription drugs; and establishment of a Center for Medicare Innovation at the CMS to test innovative payment and service delivery models to lower Medicare and Medicaid spending. Since its enactment, the U.S. federal government has delayed or suspended implementation of certain provisions of the ACA. In addition, there have been judicial and Congressional challenges to certain aspects of the ACA, and Napo expects there will be additional challenges and amendments to the ACA in the future. For example, in January 2017, the U.S. House of Representatives and Senate passed legislation, which, if signed into law, would repeal certain aspects of the ACA. In addition, Congress could consider subsequent legislation to replace those elements of the ACA if so repealed.

Napo expects that the ACA, as well as other healthcare reform measures that may be adopted in the future, may result in more rigorous coverage criteria and lower reimbursement, and additional downward pressure on the price that Napo receives for any approved product. Any reduction in reimbursement from Medicare or other government-funded programs may result in a similar reduction in payments from private payors. Moreover, recently there has been heightened governmental scrutiny over the manner in which manufacturers set prices for their marketed products. The implementation of cost containment measures or other healthcare reforms may prevent Napo from being able to generate revenue, attain profitability or commercialize Napo's drugs.

Additionally, on August 2, 2011, the Budget Control Act of 2011 created measures for spending reductions by Congress. A Joint Select Committee on Deficit Reduction, tasked with recommending a targeted deficit reduction of at least \$1.2 trillion for the years 2013 through 2021, was unable to reach required goals, thereby triggering the legislation's automatic reduction to several government programs. This included aggregate reductions of Medicare payments to providers of 2% per fiscal year, which went

Table of Contents

into effect on April 1, 2013 and, due to subsequent legislative amendments to the statute, will stay in effect through 2025 unless additional action is taken by Congress. On January 2, 2013, the American Taxpayer Relief Act of 2012 was signed into law, which, among other things, further reduced Medicare payments to several types of providers, including hospitals, imaging centers and cancer treatment centers, and increased the statute of limitations period for the government to recover overpayments to providers from three to five years. More recently, there has been heightened governmental scrutiny recently over the manner in which manufacturers set prices for their marketed products, which have resulted in several recent Congressional inquiries and proposed bills designed to, among other things, bring more transparency to product pricing, review the relationship between pricing and manufacturer patient programs, and reform government program reimbursement methodologies for pharmaceutical products.

Napo expects that additional state and federal healthcare reform measures will be adopted in the future, any of which could limit the amounts that federal and state governments will pay for healthcare products and services, which could result in reduced demand for Napo's products once approved or additional pricing pressures.

***Animal Health Business***

The development, approval and sale of animal health products are governed by the laws and regulations of each country in which we intend to seek approval, where necessary, to market and subsequently sell our prescription drug and non-drug products. To comply with these regulatory requirements, we are establishing processes and resources to provide oversight of the development, approval processes and launch of its products and to position those products in order to gain market share in each respective market.

***United States***

Certain federal regulatory agencies are charged with oversight and regulatory authority of animal health products in the United States. These agencies, depending on the product and its intended use may include the FDA, the USDA and the Environmental Protection Agency. In addition, the Drug Enforcement Administration regulates animal therapeutics that are classified as controlled substances. In addition, the Federal Trade Commission may in the case of non-drug products, regulate the marketing and advertising claims being made.

The approval of prescription drugs intended for animal use is regulated by the FDA's Center for Veterinary Medicine ("CVM"). The CVM consists of six offices that work together to, in part, approve new drugs for commercialization and thereafter monitor those commercialized drugs once in the market. The Office of New Animal Drug Evaluation ("ONADE"), is the lead office for reviewing novel drug candidates. We, as the sponsor of a novel drug candidate, commence the development and approval process by initiating communication with the ONADE and opening an INAD file. As part of this process, we will also schedule a discussion of the novel drug's development plan in order to obtain agreement from the CVM for the number, type and design of studies needed to obtain FDA approval of the novel drug.

As required by the FDA, new animal drug products must obtain marketing approval through the NADA process. Under the Administrative New Animal Drug Application, or Administrative NADA, process, a sponsor can engage in a phased submission of the required technical sections of an NADA, known as a rolling NADA, as opposed to submitting the entire application at once with a standard NADA. The requirements for all NADAs are the same regardless of whether a sponsor chooses the rolling NADA or the standard NADA submission. Under the phased review, once all technical sections have been submitted and reviewed, the sponsor submits an Administrative NADA to reflect that all technical sections of the NADA have been submitted and reviewed, each such technical section meets the requirements for approval and the CVM has issued technical section complete letters for each technical section. The phased review and Administrative NADA allow a drug sponsor to engage with the FDA as to each technical section to ensure that each section meets all requirements prior to submission of the application for approval. Phasing of NADA submissions is a voluntary process.

Table of Contents

Once the tasks set forth in the development plan have been completed, including the clinical work as well as the chemistry and manufacturing work (feasibility, validation and stability of the drug inclusive), We, as the novel drug sponsor will need to provide to the FDA through the application process, information as to the safety and efficacy of the drug candidate, and, if needed, human food safety studies. These food safety studies are only required for drugs intended for use in production animals, and we currently have no plans to develop drugs for production animals. Additionally, the application will contain a module on CMC, which describes the plan for manufacturing the drug including the API, the final formulation, where it will be made, how it will be made, how the drug will be packaged, how it can be stored, the conditions required for storage and how long it can be stored before expiry. A major part of the CMC section is the analysis we employ to ensure that the manufactured drug is of a high quality, is consistently manufactured under cGMP and is stable. Other significant components to the application we have to complete before receiving drug approval includes a draft label that will list specific information such as dosing information, intended use, warnings, directions for use, and other information as required by the regulations. The package insert that will contain information on studies, warnings, drug interactions, intended use and dosing is considered part of the label in addition to that which is adhering to the container itself. The CVM ensures that the labeling provides all the necessary information to use the drug safely and effectively, and that it clearly discloses the risks associated with the drug.

**MUMS Designation**

The Minor Use and Minor Species Animal Health Act ("MUMS Act"), became effective in August 2004. The purpose of the MUMS Act was twofold: first, to encourage the development and availability of more animal drugs that are intended to be used in a major species defined as dogs, cats, cattle, horses, chickens, turkeys and pigs to treat diseases which occur infrequently or in limited geographic areas, therefore having an impact on a smaller number of animals on a yearly basis; and second, to encourage the development and availability of animal drugs for use in minor species (defined as all animals other than humans that are not one of the major species). The drug sponsor may seek conditional approval of the drug product provided the Office of Minor Use Minor Species ("OMUMS") acknowledges that the intended use fits within a small number of animals treated per annum. A drug does not have to be designated to be eligible for conditional approval, however if OMUMS designates a MUMS drug, certain incentives and exclusivities are available to the sponsor. The MUMS designation is modeled on the orphan drug designation for human drug development and has certain financial incentives available to encourage MUMS drug development such as the availability of grants to help with the cost of the MUMS drug development. Also, drug developers of MUMS drugs are eligible to apply for a waiver of the user fees once the MUMS designation has been given by OMUMS. We believe that we qualify for MUMS designation for Canalevia as a minor use in a major species because the estimated total number of dogs in the United States affected by CID is less than 70,000. We also believe that Canalevia will qualify for MUMS designation for EID because, in our estimate, the total number of dogs in the United States affected by EID on an annual basis is less than 70,000. To obtain conditional approval of a MUMS drug, the company must submit CMC and safety data similar to that required for an NADA, as well as data suggesting a reasonable expectation of effectiveness. After the submission and the review of the application, the FDA through the CVM can then grant a conditional approval (CA-1). This approval allows for a commercialization of the product, while the sponsor continues to collect the substantial evidence of effectiveness required for a full NADA approval. The sponsor has up to five years to demonstrate substantial evidence of effectiveness for a previously conditionally approved drug. Ideally, MUMS designation helps move the product forward in development; however, it may not shorten the time to full commercialization. A sponsor that gains approval or conditional approval for a MUMS designated drug receives seven years of marketing exclusivity.

Table of Contents

**Protocol Concurrence**

As we announced in April 2016, we obtained protocol concurrence from the FDA for our pivotal trial of Canalevia that we initiated in December 2015 for acute diarrhea in dogs. We plan to pursue protocol concurrences from the FDA for future pivotal trials in other indications. Under this process, a protocol is submitted to the FDA voluntarily by a drug sponsor. The FDA review of the protocol for a pivotal study makes it more likely that the study will generate information the sponsor needs to demonstrate whether the drug is safe and effective for its intended use. It creates an expectation by the sponsor that the FDA will not later alter its perspectives on these issues unless public or animal health concerns appear that were not recognized at the time of protocol assessment. Even if FDA issues a protocol concurrence, ultimate approval of an NADA by the FDA is not guaranteed because a final determination that the agreed-upon protocol satisfies a specific objective, such as the demonstration of efficacy, or supports an approval decision, will be based on a complete review of all the data submitted to the FDA. Even if we were to obtain protocol concurrence, such concurrence does not guarantee that the results of the study will support a particular finding or approval of the new drug.

**Marketing Exclusivity**

We are currently planning on seeking MUMS designation for some of our prescription drug products and if we receive such a designation, we will be entitled to a seven-year marketing exclusivity, which means that we will face no competition from another sponsor marketing the same drug in the same dosage form for the same intended use. If we were to lose such designation or not receive such designation but our application as a new animal drug is found to be a new chemical entity that meets the criteria described by the FDA, we would be entitled to a five-year marketing exclusivity. In order to receive this five-year exclusivity, the FDA would have to find in its approval of our application that our NADA contains an API not previously approved in another application, that the application itself is an original application, not a supplemental application, and that our application included the following studies: one or more investigations to demonstrate substantial evidence of effectiveness of the drug for which we are seeking approval; animal safety studies and human food safety studies (where applicable). If the NADA is seeking approval of a drug for which we have received conditional approval, we, upon approval would still be entitled to a five-year marketing exclusivity provided we meet the criteria as set forth above. If, however, our NADA is for a drug for which the FDA has determined that the drug contains an API that has previously been approved, regardless of whether the original approval was for use in humans or not, we may only be entitled to a three-year marketing exclusivity provided that the NADA is an original, not supplemental, application and contains both safety and efficacy studies demonstrating the safety and efficacy of the drug which is the subject of the application. We have received MUMS designation for Canalevia for the indication of chemotherapy-induced diarrhea, or CID, in dogs. Additionally, the FDA has indicated that the use of Canalevia for the treatment of EID in dogs qualifies as a "minor use", which means that Canalevia is eligible for conditional approval for the indication of EID in dogs. If Canalevia is approved for CID and EID in dogs, we expect to conduct the commercial launch of Canalevia for these indications in the first half of 2018.

***European Union***

The European Union, or EU, definition of a veterinary medicinal product closely matches the definition of an animal drug in the United States. In the EU, a company can market a veterinary medicinal product only after a marketing authorization has been issued by an EU member state, (*i.e.*, approval on a country-by-country basis) or by the EU Commission through the European Medicines Agency, or the EMA. Before the EU member state or the EU Commission issues marketing authorization, we must submit a marketing authorization application, known as the dossier. The dossier includes data from studies showing the product's quality, safety, and efficacy and is similar to an NADA filed with the FDA.

Table of Contents

For an animal drug, the Committee for Medicinal Products for Veterinary Use ("CVMP"), is responsible for the scientific evaluation. Experts from all EU member states are on the CVMP. The Rapporteur, or lead reviewer on the dossier, prepares an overview of the committee's scientific evaluation, called the CVMP Assessment Report.

The CVMP Assessment Report:

summarizes the data submitted by the company on the product's quality, safety, and efficacy;

explains the assessment done by the CVMP to support the committee's recommendation to the EU Commission to issue a marketing authorization; and

is the basis for the European Public Assessment Report published on the EMA's website.

***Labeling***

The FDA plays a significant role in regulating the labeling, advertising and promotion of animal drugs. This is also true of regulatory agencies in the EU and other territories. In addition, advertising and promotion of animal health products is controlled by regulations in many countries. These rules generally restrict advertising and promotion to those claims and uses that have been reviewed and approved by the applicable agency. We will conduct a review of advertising and promotional material for compliance with the local and regional requirements in the markets where it eventually may sell its product candidates.

Our non-prescription products will be labeled in accordance with the health guidelines outlined by the National Animal Supplements Council, an industry organization that sets industry standards for certain non-prescription animal products, including but not limited to product labeling.

***Other Regulatory Considerations***

We believe regulatory rules relating to human food safety, food additives, or drug residues in food will not apply to the products we currently are developing because our animal prescription drug product candidates are not intended for use in production animals, with the exception of horses, which qualify as food animals in Europe and Canada; and our non-prescription products are not regulated by section 201(g) of the Federal Food, Drug, and Cosmetic Act, which the FDA is authorized to administer.

Our animal prescription drug product candidates currently in development, if approved, may eventually face generic competition in the United States and in the EU after the period of exclusivity has expired. In the United States, a generic animal drug may be approved pursuant to an abbreviated new animal drug application ("ANADA"). With an ANADA, a generic applicant is not subject to the submission of new clinical and safety data but instead must only show that the proposed generic product is a copy of the novel drug product, and bioequivalent to the approved novel product. However, if our product candidates are the first approved by the FDA or the EMA as applicable for use in animals, they will be eligible for a five-year marketing exclusivity in the United States and 10 years in the EU thereby prohibiting generic entry into the market. If the product has MUMS designation it has a seven-year marketing exclusivity.

We do not believe that our animal non-prescription products are currently subject to regulation in the United States. The CVM only regulates those animal supplements that fall within the FDA's definition of an animal drug, food or feed additive. The Federal Food Drug and Cosmetic Act defines food as "articles used for food or drink for man or other animals and articles used as components of any such article." Animal foods are not subject to pre-market approval and are designed to provide a nutritive purpose to the animals that receive them. Feed additives are defined as those articles that are added to an animal's feed or water as illustrated by the guidance documents. Our non-prescription products are not added to food, are not ingredients in food nor are they added to any animal's drinking water. Therefore, our non-prescription products do not fall within the definition of a food or feed additive. The FDA seeks to

Table of Contents

regulate such supplements as food or food additives depending on the intended use of the product. The intended use is demonstrated by how the article is included in a food, or added to the animals' intake (*i.e.*, through its drinking water). If the intended use of the product does not fall within the proscribed use making the product a food, it cannot be regulated as a food. There is no intent to make our non-prescription products a component of an animal food, either directly or indirectly. A feed additive is a product that is added to a feed for any reason including the top dressing of an already prepared feed. Some additives, such as certain forage, are deemed to be Generally Recognized as Safe ("GRAS"), and therefore, not subject to a feed Additive Petition approval prior to use. However, the substances deemed GRAS are generally those that are recognized as providing nutrients as a food does. We do not believe that our non-prescription products fit within this framework either. Finally, a new animal drug refers to drugs intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in animals. Our non-prescription products are not intended to diagnose, cure, mitigate, treat or prevent disease and therefore, do not fit within the definition of an animal drug. Our non-prescription products are intended to support a healthy gut, support fluid retention, and normalize stool formation in animals suffering from scours. Additionally, because a previously marketed human formulation of the botanical extract in our non-prescription products was considered a dietary supplement subject to the Dietary Supplement Health and Education Act of 1994 (and not regulated as a drug by the FDA), we do not believe that the FDA would regulate the animal formulation used in our non-prescription products in a different manner. We do not believe that our non-prescription products fit the definition of an animal drug, food or food additive and therefore are not regulated by the FDA at this time.

In addition to the foregoing, we may be subject to state, federal and foreign healthcare and/or veterinary medicine laws, including but not limited to anti-kickback laws, as we may from time to time enter consulting and other financial arrangements with veterinarians, who may prescribe or recommend our products. If our financial relationships with veterinarians are found to be in violation of such laws that apply to us, we may be subject to penalties.

**Legal Proceedings**

From time to time, we may become involved in litigation relating to claims arising from the ordinary course of business. Other than as set forth below, there are currently no claims or actions pending against us, the ultimate disposition of which could have a material adverse effect on our results of operations, financial condition or cash flows.

On July 20, 2017, a putative class action complaint was filed in the United States District Court, Northern District of California, Civil Action No. 3:17-cv-04102, by Tony Plant on behalf of pre-Merger shareholders of Jaguar who held shares on June 30, 2017 and were entitled to vote at the 2017 Special Shareholders Meeting, against us and certain individuals who were directors as of the date of the vote, in a matter captioned Tony Plant v. Jaguar Animal Health, Inc., et al. The plaintiff attempts to assert claims arising under Section 14(a) and Section 20(a) of the Exchange Act and Rule 14a-9, 17 C.F.R. § 240.14a-9, promulgated thereunder by the SEC. The plaintiff alleges that material omissions and misstatements were contained in the Joint Proxy Statement/Prospectus on Form S-4 (File No. 333-217364) declared effective by the SEC on July 6, 2017 related to the solicitation of votes from shareholders to approve the Merger and certain transaction related thereto. We believe the claims are without merit. While no monetary damages have been quantified, we intend to vigorously contest this complaint, and we've now filed a motion to have the complaint dismissed.

The plaintiff has not yet served the complaint and summons on any of the defendants. If plaintiff elected to proceed with the litigation and made service on the defendants, the defendants would move to dismiss the complaint for failure to state a claim on which relief may be granted.

Table of Contents

**Corporate Information**

We were incorporated in the State of Delaware on June 6, 2013. Our principal executive offices are located at 201 Mission Street, Suite 2375, San Francisco, CA 94015 and our telephone number is (415) 371-8300. Our website address is www.jaguar.health. The information contained on, or that can be accessed through, our website is not part of this prospectus. Our voting common stock is listed on the NASDAQ Capital Market and trades under the symbol "JAGX." On July 31, 2017, we completed the acquisition of Napo (the "Merger") pursuant to the Agreement and Plan of Merger, dated March 31, 2017, by and among the Company, Napo, Napo Acquisition Corporation, and Napo's representative (the "Merger Agreement").

Jaguar Health, our logo, Napo Pharmaceuticals, Mytesi, Canalevia, Equilevia and Neonorm are our trademarks that are used in this prospectus. This prospectus also includes trademarks, tradenames and service marks that are the property of other organizations. Solely for convenience, trademarks and tradenames referred to in this prospectus 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.

**Employees**

As of December 31, 2017, we had 36 employees. Of our employees, six hold D.V.M. or Ph.D. degrees and fifteen of our employees are engaged in research and development activities. None of our employees are represented by labor unions or covered by collective bargaining agreements.

**Description of Properties**

Our corporate headquarters are located in San Francisco, California, where we sublease 6,008 rentable square feet of office space from SeeChange Health Management Company, Inc. Our sublease agreement expires on August 31, 2018. We believe that our existing facilities are adequate for our near-term needs. We believe that suitable additional or alternative space would be available if required in the future on commercially reasonable terms if we are not able to convert our current sublease to a lease by August 31, 2018 on commercially reasonable terms.

Table of Contents

**ITEM 1A. RISK FACTORS**

The business, financial condition and operating results of the Company may be affected by a number of factors, whether currently known or unknown, including but not limited to those described below. Any one or more of such factors could directly or indirectly cause the Company's actual results of operations and financial condition to vary materially from past or anticipated future results of operations and financial condition. Any of these factors, in whole or in part, could materially and adversely affect the Company's business, financial condition, results of operations and stock price. The following information should be read in conjunction with Part II, Item 7, "Management's Discussion and Analysis of Financial Condition and Results of Operations" and the consolidated financial statements and related notes in Part II, Item 8, "Financial Statements and Supplementary Data" of this Annual Report.

**Risks Related to Our Business**

*We have a limited operating history, expect to incur further losses as we grow and may be unable to achieve or sustain profitability. Our independent registered public accounting firm has expressed substantial doubt about our ability to continue as a going concern.*

Since formation in June 2013, our operations have been primarily limited to the research and development of our animal prescription drug product candidate, Canalevia, to treat various forms of diarrhea in dogs, our non-prescription product, Neonorm Calf, to help dairies and calf farms proactively retain fluid in calves, the ongoing commercialization of Neonorm Foal, our antidiarrheal for newborn horses, and Equilevia, our planned product for total gut health in high-performance equine athletes. Since the consummation of the Merger on July 31, 2017, our operations have also been heavily focused on research, development and the ongoing commercialization of our lead prescription drug product candidate, Mytesi, which is approved by the U.S. FDA for the symptomatic relief of noninfectious diarrhea in adults with HIV/AIDS on antiretroviral therapy. As a result, we have limited meaningful historical operations upon which to evaluate our business and prospects and have not yet demonstrated an ability to broadly commercialize any of our animal health products, obtain any required marketing approval for any of our animal prescription drug product candidates or successfully overcome the risks and uncertainties frequently encountered by companies in emerging fields such as the animal health industry or the gastrointestinal health industry in general. We also have not generated any material revenue to date, and expect to continue to incur significant research and development and other expenses. Our net loss and comprehensive loss for the year ended December 31, 2017 was \$22.0 million. As of December 31, 2017, we had total stockholders' equity of \$17.3 million. We expect to continue to incur losses for the foreseeable future, which will increase significantly from historical levels as we expand our product development activities, seek necessary approvals for our human and veterinary drug product candidates, conduct species-specific formulation studies for our non-prescription products and begin commercialization activities. Even if we succeed in developing and broadly commercializing one or more of our products or product candidates, we expect to continue to incur losses for the foreseeable future, and we may never become profitable. If we fail to achieve or maintain profitability, then we may be unable to continue our operations at planned levels and be forced to reduce or cease operations.

As more fully discussed in Note 1 to our financial statements, we believe there is substantial doubt about our ability to continue as a going concern as we do not currently have sufficient cash resources to fund our operations through March 31, 2019, or one year from the filing date of our Form 10-K. Our financial statements do not include any adjustments that may result from the outcome of this uncertainty. If we are unable to continue as a viable entity, our stockholders may lose their entire investment.

*We currently generate limited revenue from the sale of products and may never become profitable.*

We are a natural-products pharmaceuticals company focused on the development and commercialization of novel, sustainably derived gastrointestinal products for both human prescription use



Table of Contents

and animals on a global basis. Napo, our wholly-owned subsidiary, began the commercial pre-launch activities of our first FDA approved product, Mytesi, in February 2017. Accordingly, we have only generated limited revenue from product sales. There is no guarantee that our ongoing commercialization efforts for Neonorm Calf for preweaned dairy calves in the United States and Neonorm Foal for newborn horses in the United States will be successful or that we will be able to generate a consistent revenue stream from the sale of any of these products in the future. Further, in order to commercialize our other prescription drug product candidates, we must receive regulatory approval from the FDA in the United States and other regulatory agencies in various jurisdictions. Other than Mytesi, we have not yet received any regulatory approvals for our prescription drug product candidates. In addition, certain of our non-prescription products, such as Neonorm Calf, may be subject to regulatory approval outside the United States prior to commercialization in other countries. Accordingly, until and unless we receive any necessary regulatory approvals, we cannot market or sell our products in many regions. Moreover, even if we receive the necessary approvals, we may not be successful in generating revenue from sales of our products as we do not have any meaningful experience marketing or distributing our products. Accordingly, we may never generate any material revenue from our operations.

***We expect to incur significant additional costs as we continue commercialization efforts for current prescription drug candidates, Neonorm, or other product candidates, and undertake the clinical trials necessary to obtain any necessary regulatory approvals, which will increase our losses.***

We commenced sales of Neonorm for preweaned dairy calves in the United States under the brand name Neonorm Calf at the end of 2014, and Napo commenced sales of Mytesi for adults with HIV/AIDS on antiretroviral therapy in February 2017. We will need to continue to invest in developing our internal and third-party sales and distribution network and outreach efforts to key opinion leaders in the gastrointestinal health industry, including physicians and veterinarians, as applicable. We will also need to conduct clinical trials for Canalevia in order to obtain necessary initial regulatory approvals and to subsequently broaden Mytesi to additional indications and Canalevia to additional indications and additional species. We will also need to conduct species-specific testing with Neonorm to expand to additional animal populations.

We are actively identifying additional products for development and commercialization, and will continue to expend substantial resources for the foreseeable future to develop Mytesi, Equilevia, Canalevia and Neonorm and develop products from Napo's library of over 2,300 medicinal plants. These expenditures will include costs associated with:

identifying additional potential prescription drug product candidates and non-prescription products;

formulation studies;

conducting pilot, pivotal and toxicology studies;

completing other research and development activities;

payments to technology licensors;

maintaining our intellectual property;

obtaining necessary regulatory approvals;

establishing commercial supply capabilities; and

sales, marketing and distribution of our commercialized products.

We also may incur unanticipated costs in connection with developing and commercializing our products. Because the outcome of our development activities and commercialization efforts is inherently



Table of Contents

uncertain, the actual amounts necessary to successfully complete the development and commercialization of our current or future products and product candidates may be greater than we anticipate.

Because we anticipate incurring significant costs for the foreseeable future, if we are not successful in broadly commercializing any of our current or future products or product candidates or raising additional funding to pursue our research and development efforts, we may never realize the benefit of our development efforts and our business may be harmed.

***We will need to raise substantial additional capital in the future in the event that we conduct clinical trials for new indications and we may be unable to raise such funds when needed and on acceptable terms, which would force us to delay, limit, reduce or terminate one or more of our product development programs.***

We are forecasting continued losses and negative cash flows as we continue to fund our operating and marketing activities and research and development programs, and we will not have sufficient cash on hand to fund our operating plan through March 31, 2019 and to complete the development of all the current products in our pipeline, or any additional products we may identify. We will need to seek additional funds sooner than planned through public or private equity or debt financings or other sources such as strategic collaborations. Any such financings or collaborations may result in dilution to our stockholders, the imposition of debt covenants and repayment obligations or other restrictions that may harm our business or the value of our common stock. We may also seek from time to time to raise additional capital based upon favorable market conditions or strategic considerations such as potential acquisitions or potential license arrangements.

Our future capital requirements depend on many factors, including, but not limited to:

the scope, progress, results and costs of researching and developing our current and future prescription drug product candidates and non-prescription products;

the timing of, and the costs involved in, obtaining any regulatory approvals for our current and any future products;

the number and characteristics of the products we pursue;

the cost of manufacturing our current and future products and any products we successfully commercialize;

the cost of commercialization activities for Mytesi, Neonorm, Equilevia and Canalevia, if approved, including sales, marketing and distribution costs;

the expenses needed to attract and retain skilled personnel;

the costs associated with being a public company;

our ability to establish and maintain strategic collaborations, distribution or other arrangements and the financial terms of such agreements; and

the costs involved in preparing, filing, prosecuting, maintaining, defending and enforcing possible patent claims, including litigation costs and the outcome of any such litigation.

Additional funds may not be available when we need them on terms that are acceptable to us, or at all. If adequate funds are not available to us on a timely basis, we may be required to delay, limit, reduce or terminate one or more of our product development programs or future commercialization efforts.



Table of Contents

***We are substantially dependent on the success of our current lead prescription drug product candidates, Mytesi and Canalevia, and our non-prescription products, Equilevia and Neonorm, and cannot be certain that necessary approvals will be received for planned Mytesi follow-on indications or Canalevia or that these product candidates will be successfully commercialized, either by us or any of our partners.***

Other than Mytesi, we currently do not have regulatory approval for any of our prescription drug product candidates, including Canalevia. Our current efforts are primarily focused on the ongoing commercialization of Mytesi, Neonorm Calf and Neonorm Foal in the United States, and development efforts related to Mytesi, Equilevia, and Canalevia, and on the development of formulations of Neonorm for additional species. With regard to Mytesi, we are focused on the commercial launch of the product in the United States as well as on development efforts related to a follow-on indication for Mytesi in CID, an important supportive care indication for patients undergoing primary or adjuvant chemotherapy for cancer treatment. Mytesi is also in development for rare disease indications for infants and children with congenital diarrheal disorders and short bowel syndrome; for IBS (Mytesi has demonstrated benefit to IBS-D patients in published Phase 2 studies); for supportive care for IBD; and as a second-generation anti-secretory agent for use in cholera patients. Mytesi has received orphan-drug designation for SBS. Accordingly, our near term prospects, including our ability to generate material product revenue, obtain any new financing if needed to fund our business and operations or enter into potential strategic transactions, will depend heavily on the success of Mytesi, Equilevia and Neonorm, as well as on Canalevia, if Canalevia is approved.

Substantial time and capital resources have been previously devoted by third parties in the development of crofelemer, the active pharmaceutical ingredient, or API, in Mytesi and Canalevia, and the development of the botanical extract used in Equilevia and Neonorm. Both crofelemer and the botanical extract used in Equilevia and Neonorm were originally developed at Shaman Pharmaceuticals, Inc. ("Shaman"), by certain members of our management team, including Lisa A. Conte, our chief executive officer and president, and Steven R. King, Ph.D., our executive vice president of sustainable supply, ethnobotanical research and intellectual property and secretary. Shaman spent significant development resources before voluntarily filing for bankruptcy in 2001 pursuant to Chapter 11 of the U.S. Bankruptcy Code. The rights to crofelemer and the botanical extract used in Equilevia and Neonorm, as well as other intellectual property rights, were subsequently acquired by Napo from Shaman in 2001 pursuant to a court approved sale of assets. Ms. Conte founded Napo in 2001 and was the current interim chief executive officer of Napo and a member of Napo's board of directors prior to the Merger. While at Napo, certain members of our management team, including Ms. Conte and Dr. King, continued the development of crofelemer. In 2005, Napo entered into license agreements with Glenmark and Luye Pharma Group Limited for rights to various human indications of crofelemer in certain territories as defined in the respective license agreements with these licensees. Subsequently, after expending significant sums developing crofelemer, including trial design and on-going patient enrollment in the final pivotal Phase 3 trial for crofelemer for non-infectious diarrhea in adults with HIV/AIDS on antiretroviral therapy, in late 2008, Napo entered into a collaboration agreement with Salix Pharmaceuticals, Inc., or Salix, for development and commercialization rights to certain indications worldwide and certain rights in North America, Europe, and Japan, to crofelemer for human use. In January 2014, Jaguar entered into the Napo License Agreement pursuant to which Jaguar acquired an exclusive worldwide license to Napo's intellectual property rights and technology, including crofelemer and the botanical extract used in Equilevia and Neonorm, for all veterinary treatment uses and indications for all species of animals. In February 2014, most of the executive officers of Napo, and substantially all Napo's employees, became Jaguar's employees. Following the merger of Jaguar and Napo in July 2017, Napo became Jaguar's wholly-owned subsidiary. If we are not successful in the development and commercialization of Mytesi, Neonorm, Equilevia and Canalevia, our business and our prospects will be harmed.

## Edgar Filing: Jaguar Health, Inc. - Form 10-K

### Table of Contents

The successful development and commercialization of Mytesi, Equilevia and Neonorm, and, if approved, Canalevia will depend on a number of factors, including the following:

the successful completion of the pivotal trials and toxicology studies for Canalevia, which may take significantly longer than we currently anticipate and will depend, in part, upon the satisfactory performance of third-party contractors;

our ability to demonstrate to the satisfaction of the FDA and any other regulatory bodies, the safety and efficacy of Canalevia;

our ability and that of our contract manufacturers to manufacture supplies of Mytesi, Neonorm, Equilevia and Canalevia and to develop, validate and maintain viable commercial manufacturing processes that are compliant with current good manufacturing practices, or cGMP, if required;

the success of Neonorm field studies and acceptance of their results by dairy producers;

our ability to successfully launch Mytesi and Neonorm, whether alone or in collaboration with others;

our ability to successfully launch Canalevia, assuming approval is obtained, and Equilevia, whether alone or in collaboration with others;

the availability, perceived advantages, relative cost, relative safety and relative efficacy of our prescription drug product candidates and non-prescription products compared to alternative and competing treatments;

the acceptance of our prescription drug product candidates and non-prescription products as safe and effective by physicians, veterinarians, patients, animal owners and the human and animal health community, as applicable;

our ability to achieve and maintain compliance with all regulatory requirements applicable to our business; and

our ability to obtain and enforce our intellectual property rights and obtain marketing exclusivity for our prescription drug product candidates and non-prescription products, and avoid or prevail in any third-party patent interference, patent infringement claims or administrative patent proceedings initiated by third parties or the U.S. Patent and Trademark Office ("USPTO").

Many of these factors are beyond our control. Accordingly, we may not be successful in developing or commercializing Mytesi, Neonorm, Equilevia, Canalevia or any of our other potential products. If we are unsuccessful or are significantly delayed in developing and commercializing Mytesi, Neonorm, Equilevia, Canalevia or any of our other potential products, our business and prospects will be harmed and you may lose all or a portion of the value of your investment in our common stock.

***If we are not successful in identifying, licensing, developing and commercializing additional product candidates and products, our ability to expand our business and achieve our strategic objectives could be impaired.***

Although a substantial amount of our efforts is focused on the commercial performance of Mytesi, Equilevia and Neonorm and the continued development and potential approval of Canalevia, a key element of our strategy is to identify, develop and commercialize a portfolio of products to serve the gastrointestinal health market. Most of our potential products are based on our knowledge of medicinal plants. Our current focus is primarily on product candidates whose active pharmaceutical ingredient or botanical extract has been successfully commercialized or demonstrated to be safe and effective in human or animal trials. In some instances, we may be unable to further develop these potential products because of perceived regulatory and commercial risks. Even if we successfully identify potential products, we may



Table of Contents

still fail to yield products for development and commercialization for many reasons, including the following:

competitors may develop alternatives that render our potential products obsolete;

an outside party may develop a cure for any disease state that is the target indication for any of our planned or approved drug products;

potential products we seek to develop may be covered by third-party patents or other exclusive rights;

a potential product may on further study be shown to have harmful side effects or other characteristics that indicate it is unlikely to be effective or otherwise does not meet applicable regulatory criteria;

a potential product may not be capable of being produced in commercial quantities at an acceptable cost, or at all; and

a potential product may not be accepted as safe and effective by physicians, veterinarians, patients, animal owners, key opinion leaders and other decision-makers in the gastrointestinal health market, as applicable.

While we are developing specific formulations, including flavors, methods of administration, new patents and other strategies with respect to our current potential products, we may be unable to prevent competitors from developing substantially similar products and bringing those products to market earlier than we can. If such competing products achieve regulatory approval and commercialization prior to our potential products, our competitive position may be impaired. If we fail to develop and successfully commercialize other potential products, our business and future prospects may be harmed and we will be more vulnerable to any problems that we encounter in developing and commercializing our current potential products.

***Mytesi faces significant competition from other pharmaceutical companies, both for its currently approved indication and for planned follow-on indications, and our operating results will suffer if we fail to compete effectively.***

The development and commercialization of products for human gastrointestinal health is highly competitive and our success depends on our ability to compete effectively with other products in the market. During the ongoing commercialization of Mytesi for its currently approved indication, and during the future commercialization of Mytesi for any planned follow-on indications, if such follow-on indications receive regulatory approval, we expect to compete with major pharmaceutical and biotechnology companies that operate in the gastrointestinal space, such as Sucampo AG, Takeda Pharmaceuticals, Allergan, Inc., Ironwood Pharmaceuticals, Inc., Synergy Pharmaceuticals Inc., Heron Therapeutics, Inc., Sebela Pharmaceuticals, Inc. and Salix Pharmaceuticals.

Many of our competitors and potential competitors in the human gastrointestinal space have substantially more financial, technical and human resources than we do. Many also have more experience in the development, manufacture, regulation and worldwide commercialization of human gastrointestinal health products.

For these reasons, we cannot be certain that we and Mytesi can compete effectively.

***Our animal health products face significant competition from other pharmaceutical companies and our operating results will suffer if we fail to compete effectively.***

The development and commercialization of animal health products is highly competitive and our success depends on our ability to compete effectively with other products in the market. We expect to



Table of Contents

compete with the animal health divisions of major pharmaceutical and biotechnology companies such as Merck Animal Health, Merial Inc., Elanco Animal Health, Bayer Animal Health GmbH, Novartis Animal Health Inc. and Boehringer Ingelheim Animal Health, as well as specialty animal health medicines companies such as Zoetis Inc., Phibro Animal Health Corporation and, in Europe, Virbac S.A., Vétquinol S.A., Ceva Animal Health S.A. and Dechra Pharmaceuticals PLC. We are also aware of several early-stage companies that are developing products for use in the animal health market, including Aratana Therapeutics, Inc., Kindred Biosciences, Inc., Parnell Pharmaceuticals Holdings Ltd, Nexvet Biopharma and ImmuCell Corporation. We also compete with academic institutions, governmental agencies and private organizations that are conducting research in the field of animal health products.

Although there are currently no FDA-approved anti-secretory products to treat chemotherapy-induced diarrhea (CID) in dogs, we anticipate that Canalevia, if approved, may face competition from various products, including products approved for use in humans that are used extra-label in animals. Extra-label use is the use of an approved drug outside of its cleared or approved indications in the animal context. All of our potential products could also face competition from new products in development. These and other potential competing products may benefit from greater brand recognition and brand loyalty than our products and product candidates may achieve.

Many of our competitors and potential competitors have substantially more financial, technical and human resources than we do. Many also have more experience in the development, manufacture, regulation and worldwide commercialization of animal health products, including animal prescription drugs and non-prescription products.

For these reasons, we cannot be certain that we and our products can compete effectively.

***We may be unable to obtain, or obtain on a timely basis, regulatory approval for our existing or future human or animal prescription drug product candidates under applicable regulatory requirements, which would harm our operating results.***

The research, testing, manufacturing, labeling, approval, sale, marketing and distribution of human and animal health products are subject to extensive regulation. We are typically not permitted to market our prescription drug product candidates in the United States until we receive approval of the product from the FDA through the filing of an NDA or NADA, as applicable. To gain approval to market a prescription drug, we must provide the FDA with safety and efficacy data from pivotal trials that adequately demonstrate that our prescription drug product candidates are safe and effective for the intended indications. Likewise, to gain approval to market an animal prescription drug for a particular species, we must provide the FDA with safety and efficacy data from pivotal trials that adequately demonstrate that our prescription drug product candidates are safe and effective in the target species (*e.g.* dogs, cats or horses) for the intended indications. In addition, we must provide manufacturing data evidencing that we can produce our product candidates in accordance with cGMP. For the FDA, we must also provide data from toxicology studies, also called target animal safety studies, and in some cases environmental impact data. In addition to our internal activities, we will partially rely on contract research organizations ("CROs"), and other third parties to conduct our toxicology studies and for certain other product development activities. The results of toxicology studies, other initial development activities, and/or any previous studies in humans or animals conducted by us or third parties may not be predictive of future results of pivotal trials or other future studies, and failure can occur at any time during the conduct of pivotal trials and other development activities by us or our CROs. Our pivotal trials may fail to show the desired safety or efficacy of our prescription drug product candidates despite promising initial data or the results in previous human or animal studies conducted by others. Success of a prescription drug product candidate in prior animal studies, or in the treatment of humans, does not ensure success in subsequent studies. Clinical trials in humans and pivotal trials in animals sometimes fail to show a benefit even for drugs that are effective because of statistical limitations in the design of the trials or other statistical

Table of Contents

anomalies. Therefore, even if our studies and other development activities are completed as planned, the results may not be sufficient to obtain a required regulatory approval for a product candidate.

Regulatory authorities can delay, limit or deny approval of any of our prescription drug product candidates for many reasons, including:

if they disagree with our interpretation of data from our pivotal studies or other development efforts;

if we are unable to demonstrate to their satisfaction that our product candidate is safe and effective for the target indication and, if applicable, in the target species;

if they require additional studies or change their approval policies or regulations;

if they do not approve of the formulation, labeling or the specifications of our current and future product candidates; and

if they fail to approve the manufacturing processes of our third-party contract manufacturers.

Further, even if we receive a required approval, such approval may be for a more limited indication than we originally requested, and the regulatory authority may not approve the labeling that we believe is necessary or desirable for successful commercialization.

Any delay or failure in obtaining any necessary regulatory approval for the intended indications of our human or animal product candidates would delay or prevent commercialization of such product candidates and would harm our business and our operating results.

***The results of our earlier studies of Mytesi and Neonorm may not be predictive of the results in any future clinical trials and species-specific formulation studies, respectively, and we may not be successful in our efforts to develop or commercialize line extensions of Mytesi and Neonorm.***

Our human and animal product pipeline includes a number of potential indications of Mytesi, our lead prescription product, and a number of species-specific formulations of Neonorm, our commercially available non-prescription product. The results of our studies and other development activities and of any previous studies in humans or animals conducted by us or third parties may not be predictive of future results of these clinical studies and formulation studies, respectively. Failure can occur at any time during the conduct of these trials and other development activities. Even if our formulation/clinical studies and other development activities are completed as planned, the results may not be sufficient to pursue a particular line extension for Mytesi or Neonorm, respectively. Further, even if we obtain promising results from our clinical trials or species-specific formulation studies, as applicable, we may not successfully commercialize any line extension. Because line extensions are developed for a particular market, we may not be able to leverage our experience from the commercial launch of Mytesi, Neonorm Calf and Neonorm Foal in new markets. If we are not successful in developing and successfully commercializing these line extension products, we may not be able to grow our revenue and our business may be harmed.

***Development of prescription drug products is inherently expensive, time-consuming and uncertain, and any delay or discontinuance of our current or future pivotal trials would harm our business and prospects.***

Development of prescription drug products for human and animal gastrointestinal health remains an inherently lengthy, expensive and uncertain process, and our development activities may not be successful. We do not know whether our current or planned pivotal trials for any of our product candidates will begin or conclude on time, and they may be delayed or discontinued for a variety of reasons, including if we are unable to:

address any safety concerns that arise during the course of the studies;

complete the studies due to deviations from the study protocols or the occurrence of adverse events;



Table of Contents

add new study sites;

address any conflicts with new or existing laws or regulations; or

reach agreement on acceptable terms with study sites, which can be subject to extensive negotiation and may vary significantly among different sites.

Further, we may not be successful in developing new indications for Mytesi and/or species-specific formulations for Neonorm, and Neonorm may be subject to the same regulatory regime as prescription drug products in jurisdictions outside the United States. Any delays in completing our development efforts will increase our costs, delay our development efforts and approval process and jeopardize our ability to commence product sales and generate revenue. Any of these occurrences may harm our business, financial condition and prospects. In addition, factors that may cause a delay in the commencement or completion of our development efforts may also ultimately lead to the denial of regulatory approval of our product candidates which, as described above, would harm our business and prospects.

***We will partially rely on third parties to conduct our development activities. If these third parties do not successfully carry out their contractual duties, we may be unable to obtain regulatory approvals or commercialize our current or future human or animal product candidates on a timely basis, or at all.***

We will partially rely upon CROs to conduct our toxicology studies and for other development activities. We intend to rely on CROs to conduct one or more of our planned pivotal trials. These CROs are not our employees, and except for contractual duties and obligations, we have limited ability to control the amount or timing of resources that they devote to our programs or manage the risks associated with their activities on our behalf. We are responsible for ensuring that each of our studies is conducted in accordance with the development plans and trial protocols presented to regulatory authorities. Any deviations by our CROs may adversely affect our ability to obtain regulatory approvals, subject us to penalties or harm our credibility with regulators. The FDA and foreign regulatory authorities also require us and our CROs to comply with regulations and standards, commonly referred to as good clinical practices ("GCPs"), or good laboratory practices ("GLPs"), for conducting, monitoring, recording and reporting the results of our studies to ensure that the data and results are scientifically valid and accurate.

Agreements with CROs generally allow the CROs to terminate in certain circumstances with little or no advance notice. These agreements generally will require our CROs to reasonably cooperate with us at our expense for an orderly winding down of the CROs' services under the agreements. If the CROs conducting our studies do not comply with their contractual duties or obligations, or if they experience work stoppages, do not meet expected deadlines, or if the quality or accuracy of the data they obtain is compromised, we may need to secure new arrangements with alternative CROs, which could be difficult and costly. In such event, our studies also may need to be extended, delayed or terminated as a result, or may need to be repeated. If any of the foregoing were to occur, regulatory approval, if required, and commercialization of our product candidates may be delayed and we may be required to expend substantial additional resources.

***Even if we obtain regulatory approval for planned follow-on indications of Mytesi, or for Canalevia or our other product candidates, they may never achieve market acceptance. Further, even if we are successful in the ongoing commercialization of Mytesi and Neonorm, we may not achieve commercial success.***

If we obtain necessary regulatory approvals for planned follow-on indications of Mytesi or for Canalevia or our other product candidates, such products may still not achieve market acceptance and may not be commercially successful. Market acceptance of Mytesi, Canalevia, Neonorm and any of our other products depends on a number of factors, including:

the safety of our products as demonstrated in our target animal studies;

the indications for which our products are approved or marketed;

Table of Contents

the potential and perceived advantages over alternative treatments or products, including generic medicines and competing products currently prescribed by physicians or veterinarians, as applicable, and, in the case of animal products, products approved for use in humans that are used extra-label in animals;

the acceptance by physicians, veterinarians, companion animal owners and production animal owners, including in the dairy industry, as applicable, of our products as safe and effective;

the cost in relation to alternative treatments and willingness on the part of physicians, veterinarians, patients and animal owners, as applicable, to pay for our products;

the prevalence and severity of any adverse side effects of our products;

the relative convenience and ease of administration of our products; and

the effectiveness of our sales, marketing and distribution efforts.

Any failure by Mytesi, Canalevia, Equilevia, Neonorm or any of our other products to achieve market acceptance or commercial success would harm our financial condition and results of operations.

***The dairy industry is subject to conditions beyond our control and the occurrence of any such conditions may harm our business and impact the demand for our products.***

The demand for production animal health products, such as Neonorm Calf, is heavily dependent on factors that affect the dairy market that are beyond our control, including the following, any of which may harm our business:

cost containment measures within the dairy industry, in response to international, national and local general economic conditions, which may affect the market adoption of our products;

state and federal government policies, including government-funded programs or subsidies whose discontinuance or modification could erode the demand for our products;

a decline in demand for dairy products due to changes in consumer diets away from dairy products, which could adversely affect the demand for production animal health products;

adverse weather conditions and natural disasters, such as floods, droughts, and pestilence, which can lower dairy yields; and

disease or other conditions beyond our control.

***Human and animal gastrointestinal health products are subject to unanticipated post-approval safety or efficacy concerns, which may harm our business and reputation.***

The success of our commercialization efforts will depend upon the perceived safety and effectiveness of human and animal gastrointestinal health products, in general, and of our products, in particular. Unanticipated safety or efficacy concerns can subsequently arise with respect to approved prescription drug products, such as Mytesi, or non-prescription products, such as Neonorm, which may result in product recalls or withdrawals or suspension of sales, as well as product liability and other claims. Any safety or efficacy concerns, or recalls, withdrawals or suspensions of sales of our products could harm our reputation and business, regardless of whether such concerns or actions are justified.

*Future federal and state legislation may result in increased exposure to product liability claims, which could result in substantial losses.*

Under current federal and state laws, companion and production animals are generally considered to be the personal property of their owners and, as such, the owners' recovery for product liability claims involving their companion and production animals may be limited to the replacement value of the animal.

Table of Contents

Companion animal owners and their advocates, however, have filed lawsuits from time to time seeking non-economic damages such as pain and suffering and emotional distress for harm to their companion animals based on theories applicable to personal injuries to humans. If new legislation is passed to allow recovery for such non-economic damages, or if precedents are set allowing for such recovery, we could be exposed to increased product liability claims that could result in substantial losses to us if successful. In addition, some horses can be worth millions of dollars or more, and product liability for horses may be very high. While we currently have product liability insurance, such insurance may not be sufficient to cover any future product liability claims against us.

***If we fail to retain current members of our senior management, or to identify, attract, integrate and retain additional key personnel, our business will be harmed.***

Our success depends on our continued ability to attract, retain and motivate highly qualified management and scientific personnel. We are highly dependent upon our senior management, particularly Lisa A. Conte, our president and Chief Executive Officer. The loss of services of any of our key personnel would cause a disruption in our ability to develop our current or future product pipeline and commercialize our products and product candidates. Although we have offer letters with these key members of senior management, such agreements do not prohibit them from resigning at any time. For example, the resignation of our former Chief Financial Officer, Charles O. Thompson, in September 2014, and the mutually agreed departure of our former Chief Veterinary Officer, Serge Martinod, D.V.M., Ph.D. in February 2015, caused us to incur additional expenses and expend resources to ensure a smooth transition with their respective successors, which diverted management attention away from executing our operational plan during this period. We currently do not maintain "key man" life insurance on any of our senior management team. The loss of Ms. Conte or other members of our current senior management could adversely affect the timing or outcomes of our current and planned studies, as well as the prospects for commercializing our products.

In addition, competition for qualified personnel in the human and animal gastrointestinal health fields is intense, because there are a limited number of individuals who are trained or experienced in the field. Further, our headquarters are located in San Francisco, California, and the dairy and agriculture industries are not prevalent in urban areas such as San Francisco. We will need to hire additional personnel as we expand our product development and commercialization activities. Even if we are successful in hiring qualified individuals, as we are a growing organization, we do not have a track record for integrating and retaining individuals. If we are not successful in identifying, attracting, integrating or retaining qualified personnel on acceptable terms, or at all, our business will be harmed.

***We are dependent on two suppliers for the raw material used to produce the active pharmaceutical ingredient in Mytesi and Canalevia and the botanical extract in Neonorm and Equilevia. The termination of either of these contracts would result in a disruption to product development and our business will be harmed.***

The raw material used to manufacture Mytesi, Canalevia, Neonorm and Equilevia is crude plant latex ("CPL"), derived from the *Croton lechleri* tree, which is found in countries in South America, principally Peru. The ability of our contract suppliers to harvest CPL is governed by the terms of their respective agreements with local government authorities. Although CPL is available from multiple suppliers, we only have contracts with two suppliers to obtain CPL and arrange the shipment to our contract manufacturer. Accordingly, if our contract suppliers do not or are unable to comply with the terms of our respective agreements, and we are not able to negotiate new agreements with alternate suppliers on terms that we deem commercially reasonable, it may harm our business and prospects. The countries from which we obtain CPL could change their laws and regulations regarding the export of the natural products or impose or increase taxes or duties payable by exporters of such products. Restrictions could be imposed on the harvesting of the natural products or additional requirements could be implemented for the replanting and regeneration of the raw material. Such events could have a significant impact on our cost and ability to produce Mytesi, Canalevia, Neonorm, Equilevia and anticipated line extensions.

Table of Contents

***We are dependent upon third-party contract manufacturers, both for the supply of the active pharmaceutical ingredient in Mytesi and Canalevia and the botanical extract in Neonorm and Equilevia, as well as for the supply of finished products for commercialization.***

We have contracted with third parties for the formulation of API and botanical extract into finished products for our studies. We have also entered into memorandums of understanding with Indena S.p.A. for the manufacture of CPL received from our suppliers into the API in Canalevia to support our regulatory filings, as well as the botanical extract in Neonorm and agreed to negotiate a commercial supply agreement. Indena S.p.A. has never manufactured either such ingredient to commercial scale. As a second supplier situation, we have entered into a four-year manufacturing and supply agreement with Glenmark for the supply of the API in Canalevia. Glenmark is the current manufacturer of crofelemer, the active API in Canalevia, for Mytesi, and the manufacturer on file for the NADA to which we have a right of reference. As announced in October of 2015, we have entered an agreement with Patheon, a provider of drug development and delivery solutions, under which Patheon provides enteric-coated tablets to us for use in animals. We also may contract with additional third parties for the formulation and supply of finished products, which we will use in our planned studies and commercialization efforts.

We will be dependent upon our contract manufacturers for the supply of the API in Mytesi and Canalevia. We currently have sufficient quantities of the botanical extract used in Neonorm and Equilevia to support initial commercialization of Neonorm and Equilevia. However, we will require additional quantities of the botanical extract if our ongoing commercial launch of Neonorm or our commercial launch of and Equilevia is successful. If we are not successful in reaching agreements with third parties on terms that we consider commercially reasonable for manufacturing and formulation, or if our contract manufacturer and formulator are not able to produce sufficient quantities or quality of API, botanical extract or finished product under their agreements, it could delay our plans and harm our business prospects.

The facilities used by our third-party contractors are subject to inspections, including by the FDA, and other regulators, as applicable. We also depend on our third-party contractors to comply with cGMP. If our third-party contractors do not maintain compliance with these strict regulatory requirements, we and they will not be able to secure or maintain regulatory approval for their facilities, which would have an adverse effect on our operations. In addition, in some cases, we also are dependent on our third-party contractors to produce supplies in conformity to our specifications and maintain quality control and quality assurance practices and not to employ disqualified personnel. If the FDA or a comparable foreign regulatory authority does not approve the facilities of our third-party contractors if so required, or if it withdraws any such approval in the future, we may need to find alternative manufacturing or formulation facilities, which could result in delays in our ability to develop or commercialize our human and animal products, if at all. We and our third-party contractors also may be subject to penalties and sanctions from the FDA and other regulatory authorities for any violations of applicable regulatory requirements. The USDA and the European Medicines Agency (the "EMA"), employ different regulatory standards than the FDA, so we may require multiple manufacturing processes and facilities for the same human or animal product candidate or any approved product. We are also exposed to risk if our third-party contractors do not comply with the negotiated terms of our agreements, or if they suffer damage or destruction to their facilities or equipment.

***If we are unable to establish sales capabilities on our own or through third parties, we may not be able to market and sell our current or future human or animal products and product candidates, if approved, and generate product or other revenue.***

We currently have limited sales, marketing or distribution capabilities, and prior to Napo's launch of Mytesi for the symptomatic relief of noninfectious diarrhea in adults with HIV/AIDS on antiretroviral therapy, and our launch of Neonorm for preweaned dairy calves, we had no experience in the sale, marketing and distribution of human or animal health products. There are significant risks involved in



Table of Contents

building and managing a sales organization, including our potential inability to attract, hire, retain and motivate qualified individuals, generate sufficient sales leads, provide adequate training to sales and marketing personnel and effectively oversee a geographically dispersed sales and marketing team. Any failure or delay in the development of our internal sales, marketing and distribution capabilities and entry into adequate arrangements with distributors or other partners would adversely impact the commercialization of Mytesi, Neonorm, Equilevia and, if approved, Canalevia. If we are not successful in commercializing Mytesi, Neonorm, Equilevia, Canalevia or any of our other line extension products, either on our own or through one or more distributors, or in generating upfront licensing or other fees, we may never generate significant revenue and may continue to incur significant losses, which would harm our financial condition and results of operations.

***Changes in distribution channels for animal health prescription drugs may make it more difficult or expensive to distribute our animal health prescription drug products.***

In the United States, animal owners typically purchase their animal health prescription drugs from their local veterinarians who also prescribe such drugs. There is a trend, however, toward increased purchases of animal health prescription drugs from Internet-based retailers, "big-box" retail stores and other over-the-counter distribution channels, which follows an emerging shift in recent years away from the traditional veterinarian distribution channel. It is also possible that animal owners may come to rely increasingly on Internet-based animal health information rather than on their veterinarians. We currently expect to market our animal health prescription drugs directly to veterinarians, so any reduced reliance on veterinarians by animal owners could harm our business and prospects by making it more difficult or expensive for us to distribute our animal health prescription drug products.

Legislation has been or may be proposed in various states that would require veterinarians to provide animal owners with written prescriptions and disclosures that the animal owner has the right to fill the prescriptions through other means. If enacted, such legislation could lead to a reduction in the number of animal owners who purchase their animal health pharmaceuticals directly from veterinarians, which also could harm our business.

***Consolidation of our customers could negatively affect the pricing of our animal health products.***

Veterinarians will be our primary customers for our prescription animal health drug products, as well as, to some extent, our non-prescription animal health products, such as Neonorm and Equilevia. In recent years, there has been a trend towards the consolidation of veterinary clinics and animal hospitals. If this trend continues, these large clinics and hospitals could attempt to leverage their buying power to obtain favorable pricing from us and other animal health product companies. Any downward pressure on the prices of any of our animal health products could harm our operating results and financial condition.

***We will need to increase the size of our organization and may not successfully manage such growth.***

As of December 31, 2017, we had 36 full-time equivalent (FTE) employees. Our ability to manage our growth effectively will require us to hire, train, retain, manage and motivate additional employees and to implement and improve our operational, financial and management systems. These demands also may require the hiring of additional senior management personnel or the development of additional expertise by our senior management personnel. If we fail to expand and enhance our operational, financial and management systems in conjunction with our potential future growth, it could harm our business and operating results.

Table of Contents

***Research and development with respect to our animal health products and product candidates relies on evaluations in animals, which is controversial and may become subject to bans or additional regulations.***

The evaluation of our animal health products and product candidates in target animals is required to develop, formulate and commercialize our animal health products and product candidates. Although our animal testing will be subject to GLPs and GCPs, as applicable, animal testing in the human pharmaceutical industry and in other industries continues to be the subject of controversy and adverse publicity. Some organizations and individuals have sought to ban animal testing or encourage the adoption of additional regulations applicable to animal testing. To the extent that such bans or regulations are imposed, our research and development activities with respect to animal health products, and by extension our operating results and financial condition, could be harmed. In addition, negative publicity about animal practices by us or in our industry could harm our reputation among potential customers.

***If approved, our animal health prescription drug product candidates may be marketed in the United States only in the target animals and for the indications for which they are approved, and if we want to expand the approved animals or indications, it will need to obtain additional approvals, which may not be granted.***

If our animal health prescription drug product candidates are approved by regulatory authorities, we may market or advertise them only in the specific species and for treatment of the specific indications for which they were approved, which could limit use of the products by veterinarians and animal owners. We intend to develop, promote and commercialize approved products for other animals and new treatment indications in the future, but we cannot be certain whether or at what additional time and expense we will be able to do so. If we do not obtain marketing approvals for other species or for new indications, our ability to expand our animal health business may be harmed.

Under the Animal Medicinal Drug Use Clarification Act of 1994, veterinarians are permitted to prescribe extra-label uses of certain approved animal drugs and approved human drugs for animals under certain conditions. While veterinarians may in the future prescribe and use human-approved products or use our products for extra-label uses, we may not promote our animal health products for extra-label uses. We note that extra-label uses are uses for which the product has not received approval. If the FDA determines that any of our marketing activities constitute promotion of an extra-label use, we could be subject to regulatory enforcement, including seizure of any misbranded or mislabeled drugs, and civil or criminal penalties, any of which could have an adverse impact on our reputation and expose us to potential liability. We will continue to spend resources ensuring that our promotional claims for our animal health products and product candidates remain compliant with applicable FDA laws and regulations, including materials we post or link to on our website. For example, in 2012, our Chief Executive Officer received an "untitled letter" from the FDA while at Napo regarding preapproval promotion statements constituting misbranding of crotelemer, which was then an investigational drug. These statements were included in archived press releases included on Napo's website. Napo was required to expend time and resources to revise its website to remove the links in order to address the concerns raised in the FDA's letter.

***If our human or animal prescription drug product candidates are approved by regulatory authorities, the misuse or extra-label use of such products may harm our reputation or result in financial or other damages.***

If our human or animal prescription drug product candidates are approved by regulatory authorities, there may be increased risk of product liability